A Genomic Model for Predicting the Ultraviolet Susceptibility of Viruses

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ABSTRACT

A mathematical model is presented to explain the ultraviolet susceptibility of viruses in terms of genomic sequences that have a high potential for photodimerization. The specific sequences with high dimerization potential include doublets of thymine (TT), thymine-cytosine (TC), cytosine (CC), and triplets composed of single purines combined with pyrimidine doublets. The complete genomes of 49 animal viruses and bacteriophages were evaluated using base-counting software to establish the frequencies of dimerizable doublets and triplets. The model also accounts for the effects of ultraviolet scattering. Constants defining the relative lethality of the four dimer types were determined via curve-fitting. A total of 70 data sets were used to represent 27 RNA viruses. A total 77 water-based UV rate constant data sets were used to represent 22 DNA viruses. Predictions are provided for dozens of viruses of importance to human health that have not previously been tested for their UV susceptibility.

INTRODUCTION

The susceptibility of viruses to ultraviolet (UV) light has traditionally been defined in terms of the UV rate constant, also called a Z value, which is the slope of the survival curve on a logarithmic scale. The UV rate constant refers to either broad range UV in the UVB/UVC spectrum (200-320 nm) or, more commonly, to narrow-band UVC near the 253.7 nm wavelength. UV susceptibility can also be defined by the UV exposure dose (fluence) required for 90% inactivation (the D_{90} value), a more intuitive parameter that avoids the problem of defining shoulder effects and second stages in the survival curve. In this paper the UV rate constant is defined in terms of the D_{90} value to provide an absolute indicator of UV susceptibility in the first stage of decay, and these values are thereby interchangeable. The UV rate constant, in m^2/J, applicable to the first stage of decay is defined as:

$$k = \frac{-ln(S)}{D_{90}} \qquad (1)$$

where S = survival, fractional
D = UV exposure dose (fluence), J/m^2
The D_{90} value is then:

$$D_{90} = \frac{-ln(1-0.9)}{k} = \frac{-ln(0.1)}{k} = \frac{2.3026}{k} \qquad (2)$$

The subject of virus UV susceptibility has been extensively studied and the processes that occur at the molecular level have been quantified to an great degree, but the complexities of these processes and prior lack of fully sequenced genomes have heretofore precluded development of a complete quantitative model of virus inactivation. The actual theoretical basis for UV susceptibility has been elucidated in the works of Setlow and Carrier (1966), Smith and Hanawalt (1969), Becker and Wang (1989), and others. This paper applies the basic model of UV inactivation as detailed in these seminal works to viral genomes from the NCBI database (NCBI 2009) and statistically evaluates the correlation with known UV D_{90} values. With some enhancements of the basic model and adjustments to the parameters, a model is developed herein that provides predictions for both RNA and DNA viruses. This model also includes a new ultraviolet scattering model developed by the authors that contributes to the overall accuracy of the DNA model.

Rate Constant Determinants

Various intrinsic factors determine the sensitivity of a virus to UV exposure under any set of constant ambient conditions of temperature and humidity including physical size, molecular weight, DNA conformation, presence of chromophores, propensity for clumping, presence of repair enzymes or dark/light repair mechanisms, hydrophilic surface properties, relative index of refraction, specific spectrum of UV, G+C% content, and % of potential pyrimidine dimers.

The physical size of a virus bears no clear direct relationship with UV susceptibility. UV-induced damage to DNA is independent of molecular weight (Scholes et al 1967). Virus nucleocapsids are too thin to allow any significant chromophore protection. The specific UV spectrum has a

relatively minor or insignificant effect according to most studies although some differences between LP and MP lamps have been noted (Linden et al 2007), but in this study virtually all the data is based on LP lamps. Viruses have no repair enzymes and their dark/light repair mechanisms play a minor or insignificant role. Hydrophilic surface properties and propensity for clumping are largely unknown for viruses. The DNA conformation directly impacts UV susceptibility but this model treats DNA viruses in water (B conformation) separately from RNA viruses (A-conformation). The G+C% content plays an indirect role in UV susceptibility but this factor is enveloped by the more detailed approach of analyzing genomic content addressed in this model. The relative index of refraction in the UV range is not known for viruses but a general model for UV scatter is developed and incorporated in the DNA model. The RNA model has negligible UV scattering effects due to their size parameters being so small.

The UV Scattering Model

Viruses, which are about 0.02 microns and larger, are subject to ultraviolet scattering effects due to the fact that their size is very near the wavelength of ultraviolet light. The effect of scattering is to reduce the effective irradiance to which the microbe is exposed, and it is necessary to account for this attenuation if it has a major impact on reducing the UV exposure dose. The interaction between ultraviolet wavelengths and the particle is a function of the relative size of the particle compared with the wavelength, as defined by the size parameter:

$$x = \frac{2\pi a}{\lambda} \qquad (3)$$

where a = the effective radius of the particle
λ = wavelength

The scattering of light is due to differences in the refractive indices between the medium and the particle (Bohren and Huffman 1983). The scattering properties of a spherical particle in any medium are defined by the complex index of refraction:

$$m = n - i\kappa \qquad (4)$$

where n = real refractive index
κ = imaginary refractive index (absorptive index or absorption coefficient)

The process of independent Mie scattering is also governed by the relative refractive index, defined as follows:

$$m = \frac{n_s}{n_m} \qquad (5)$$

where n_s = refractive index of the particle (a microbe)
n_m = refractive index of the medium (air or water)

Readers may consult the references for further information on Mie theory (vandeHulst 1957, Bohren and Huffman 1983). The refractive index of microbes in visible light has been studied by several researchers but there are no studies that address the real refractive index of viruses at UV wavelengths. Water has a refractive index of $n_m = 1.4$ in the ultraviolet range. If the UV refractive index of viruses in visible light is scaled to that of water, the estimated real refractive index would be about 1.12 (Kowalski 2009). In fact, UV scattering effects are not sensitive to the choice of values within the range 1.03-1.45 and the choice of n=1.12 is reasonable. For the imaginary refractive index (the absorptive index) in the UV range no information is available. However, we can reasonably assume a value comparable to that of water, k=1.4, or any value in the range of the real refractive indices given above as they have even less overall impact than the real refractive index. These values were used as input to a Mie Scattering program (Prahl 2009) to estimate the effects of UV scattering at the wavelength of 253.7 nm.

The computed ratio of the scattering cross-section to the extinction cross-section represents the fraction of total irradiance that is scattered away (Kowalski et al 2009). The fraction of scattered UV is relatively minor for most RNA viruses, but increases sharply through the DNA virus size range, approaching a limit of about 0.68. The computed values for UV scatter are used to correct the incident UV irradiance (or D_{90} exposure value). Table 1 shows the

Virus	Type	Diameter μm	UV Scatter Correction	Virus	Type	Diameter μm	UV Scatter Correction
Bacteriophage MS2	DNA	0.020	0.9732	B. subtilis phage SP	DNA	0.087	0.6122
Echovirus (Parechovirus)	RNA	0.024	0.9552	Coliphage T4	DNA	0.089	0.6057
Encephalomyocarditis virus	RNA	0.025	0.9501	Borna virus	DNA	0.090	0.6026
Coxsackievirus	RNA	0.027	0.9391	Friend Murine Leukemia virus	DNA	0.094	0.5907
Hepatitis A virus	RNA	0.027	0.9391	Moloney Murine Leukemia virus	RNA	0.094	0.5907
Murine Norovirus	RNA	0.032	0.9086	Rauscher Murine Leukemia virus	RNA	0.094	0.5907
Feline Calicivirus (FCV)	DNA	0.034	0.8955	Avian Sarcoma virus	RNA	0.098	0.5798
Canine Calicivirus	RNA	0.037	0.8755	Influenza A virus	RNA	0.098	0.5798
Polyomavirus	RNA	0.042	0.8389	BLV	DNA	0.099	0.5772
Simian virus 40	RNA	0.045	0.8214	Murine Cytomegalovirus	RNA	0.104	0.5649
Coliphage lambda	RNA	0.050	0.7889	Vesicular Stomatitis virus (VSV)	RNA	0.104	0.5649
Coliphage T1	DNA	0.050	0.7889	Equine Herpes virus	RNA	0.105	0.5626
Semliki Forest virus	DNA	0.061	0.7240	Avian Leukosis virus	RNA	0.107	0.5581
Coliphage PRD1	DNA	0.062	0.7186	Coronavirus (incl SARS)	RNA	0.113	0.5457
HP1c1 phage	DNA	0.062	0.7186	Murine sarcoma virus	RNA	0.120	0.5330
Coliphage T7	DNA	0.063	0.7133	HIV-1	RNA	0.125	0.5249
Mycobacterium phage D29	DNA	0.065	0.7030	Rous Sarcoma virus (RSV)	DNA	0.127	0.5218
VEE	DNA	0.065	0.7030	Frog virus 3	RNA	0.167	0.4793
Adenovirus Type 40	RNA	0.069	0.6835	Herpes simplex virus Type 2	RNA	0.173	0.4750
Rabies virus	RNA	0.070	0.6788	Herpes simplex virus Type 1	RNA	0.184	0.4681
WEE	DNA	0.070	0.6788	Pseudorabies (PRV)	DNA	0.194	0.4626
Sindbis virus	DNA	0.075	0.6569	Newcastle Disease Virus	DNA	0.212	0.4544
Adenovirus Type 1	RNA	0.079	0.6408	Vaccinia virus	DNA	0.307	0.4280
Adenovirus Type 2	RNA	0.079	0.6408	Measles	DNA	0.329	0.4237
Adenovirus Type 5	DNA	0.084	0.6224	NOTE: Virus diameters represent logmean values.			

Table 1. *Virus Mean Diameters and UV Scattering Corrections*

diameters of the viruses used in this study and the associated UV scatter correction factors, which are later applied to the raw D_{90} values shown in Tables 3 and 4. Virus diameters were obtained from various sources (i.e. Kowalski 2006). Diameters are logmean values of the smallest dimension or logmean values of ovoid envelopes. For more detailed information on the computation of UV scattering effects see Kowalski (2009).

The Genomic Model

The effect of base composition can impact the intrinsic sensitivity of DNA to UV irradiation and the specific sequence of adjacent base pairs, as well as the frequency of thymines, are major, if not primary, determinants of UV sensitivity. The disruption of normal DNA processes occurs as the result of the formation of photodimers, but not all photoproducts appear with the same frequency. Purines are approximately ten times more resistant to photoreaction than pyrimidines (Smith and Hanawalt 1969). Minor products other than CPD dimers, such as interstrand cross-links, chain breaks, and DNA-protein links occur with much less frequency, typically less than 1/1000 of the number of cyclobutane dimers and hydrates may occur at about 1/10 the frequency of cyclobutane dimers (Setlow and Carrier 1966). Some 80% of pyrimidines and 45% or purines form UV photoproducts in double-stranded DNA, per studies by Becker and Wang (1989), who also showed that purines only form dimers when adjacent to a pyrimidine doublet. The formation of purine dimers requires transfer of energy in neighboring pyrimidines, and will only occur on the 5′ side of the purine base (a 50% probability). Becker and Wang (1985) formulated these simple rules for sequence-dependent DNA photoreactivity:

1. Whenever two or more pyrimidine residues are adjacent to one another, photoreactions are observed at both pyrimidines.
2. Non-adjacent pyrimidines, surrounded on both sides by purines, exhibit little or no photoreactivity.
3. The only purines that readily form UV photoproducts are those that are flanked on their 5′ side by two or more contiguous pyrimidine residues.

Table 2 summarizes these rules in terms that can be computed numerically. The adjacent pyrimidines are referred to as doublets and the flanked purines are called triplets. Counting of these doublets is performed exclusively (no doublets are counted twice) and in the order (left to right and top to bottom) as shown in Table 2. Other counting orders are possible, of course, but this straightforward method appears adequate.

Group	DNA Sequence				Dimer
Adjacent pyrimidines	TT	TC	CT	CC	Yes
Purines flanked by doublets	ATT	ACC	ACT	ATC	50% Yes
	GTT	GCC	GCT	GTC	50% Yes
	TTA	CCA	CTA	TCA	50% Yes
	TTG	CCG	CTG	CGT	50% Yes
Surrounded pyrimidines	ATA	ATG	GTA	GTG	No
	ACA	ACG	GCA	GCG	No

Table 2. *Potential Dimerization Sequences*

A function can be written to sum the potential dimerization values that exist within the physical volume of DNA or RNA. The volume of the sphere will be directly proportional to the genome size, since the nucleic acids are essentially packed tight inside a capsid, and because almost all animal viruses of interest are spherical, ovoid, or possess a spherical capsid atop a tail. The potential dimer density map can be viewed as points collapsed onto a circular cross-section exposed to a collimated beam of UV rays. The volume of the model sphere is equivalent to the base pairs (bp) of the genome (in bp units), and the area of the cross-section is then the cube root of the square of the base pairs, as illustrated in Figure 1.

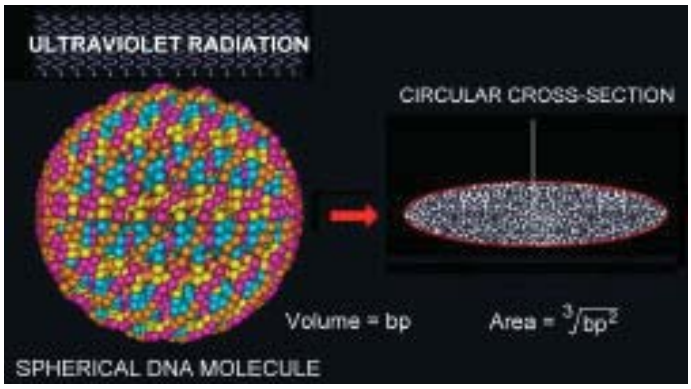

Figure 1: *The spherical model of DNA has a circular cross-section with a collapsed potential dimerization density map subject to collimated UV rays.*

RNA Virus Model

Single stranded RNA (ssRNA) viruses are the simplest structures to model and these are addressed first. The square root of the sum of the potential dimer values, counted as per Table 1, is used because it was found on analysis that this produces the best fit overall, and so without further theoretical justification the potential dimerization equation for ssRNA viruses is written:

$$D_v = \frac{\left[\sum tt + F_a \sum \overleftrightarrow{ct} + F_b \sum cc + F_c \sum \overleftrightarrow{YYU}\right]^{0.5}}{\sqrt[3]{bp^2}} \qquad (6)$$

where D_v = dimerization value

tt = thymine doublets

cc = cytosine doublets

$\overleftrightarrow{ct}$= ct and tc (counted both ways, exclusive)

$\overleftrightarrow{YYU}$= purine w/ adjacent pyrimidine doublet (counted both ways, exclusive)

bp = total base pairs

F_a, F_b, F_c = dimer proportionality constants

Some evidence is available in the literature to allow some starting estimates of the dimer proportionality constants. Per Setlow and Carrier (1966) the average for three bacteria is 1:0.25:0.13. Patrick (1977) suggests ratios of 1:1:1. Unrau (1973) found the ratio was 1:0.5:0.5. Meistrich et al (1970) indicate that in E. *coli* DNA, the proportions of TT dimers, CT dimers, and CC dimers are in the ratio 1:0.8:0.2, as did Lamola (1973). Table 3 lists 62 of the 70 virus data sets that were used in the ssRNA model, along with the average rate constants and the average D_{90} values representing 27 single-stranded RNA viruses. These D_{90} values are not adjusted for UV scatter (per the Table 2 correction factors). Only water-based test results were used since they are the most numerous and they all represent the B-DNA conformation. Data was culled exclusively from the literature and no animal virus or bacteriophage was omitted from consideration. The data sets for MS2 (marked with an asterisk in Table 3), however, were so numerous that although they were all averaged, only seven data points were credited, so as not to give undue weight to this particular phage. The remaining eight data sets for MS2 are listed in the References (Furuse and Watanabe 1971, Sommer et al 2001, Mamane-Gravetz et al 2005, Templeton et al 2006, Nuanualsuwan 2002, Rauth 1965, Shin et al 2005, Meng and Gerba 1996). Only one anomalous outlier was excluded from the 70 data sets (HTLV-1 per Shimizu et al 2004).

Table 3. *Rate Constants and D_{90} Values for RNA Viruses*

Virus	NCBI ID#	Genome bp	D_{90} J/m^2	UVGI k m^2/J	Avg k m^2/J	Avg D_{90} J/m^2	Source
Bacteriophage MS2*	NC_001699	3569	295	0.00780	0.01	237	Ko 2005
		3569	275	0.00837			Thurston-Enriquez 2003
		3569	250	0.00920			Battiggelli 1993
		3569	217	0.01060			Simonet 2006
		3569	217	0.01063			deRodaHusman 2004
		3569	213	0.01080			Butkus 2004
		3569	187	0.01230			Oppenheimer 1997
Murine sarcoma virus	NC_001502	5833	237	0.0097	0.0111	207	Nomura 1972
		5833	144	0.016			Kelloff 1970
		5833	299	0.0077			Yoshikura 1971
Coxsackievirus	NC_001612	7413	128	0.02	0.02834	81	Hill 1970
		7413	86	0.026837			Havelaar 1987
		7413	80	0.02878			Gerba 2002
		7413	60	0.03840			Shin 2005
		7413	95	0.02424			Gerba 2002
		7413	72	0.03180			Battigelli 1993
Echovirus	NC_001897	7345	106	0.02190	0.027859	83	Hill 1970
		7345	80	0.02878			Gerba 2002 (type 1)
		7345	70	0.03289			Gerba 2002 (type 2)
Feline Calicivirus (FCV)	NC_001699	7677	434	0.0053	0.030567	75	Nuanualsuwan 2002
		7677	80	0.0288			Thurston-Enriquez 2003
		7677	40	0.0576			deRodaHusman 2004
Canine Calicivirus	NC_004542	8513	67	0.0345	0.0345	67	deRodaHusman 2004
Encephalomyocarditis virus	NC_001479	7835	50	0.0465	0.0422	55	Ross 1971
		7835	52	0.0446			Rauth 1965
		7835	65	0.0355			Zavadova 1968
Influenza A virus	NC_007366-73	13498	20	0.117	0.10103	23	Ross 1971
		13498	48	0.048			Hollaender 1944
		13498	17	0.1381			Abraham 1979
Vesicular Stomatitis virus (VSV)	NC_001560	11161	13	0.1806	0.1944	12	Rauth 1965
		11161	12	0.19			Helentjaris 1977
		11161	100	0.023			Bay 1979
		11161	6	0.384			Shimizu 2004
Newcastle Disease Virus	NC_002617	15186	8	0.276	0.1636	14	vonBrodorotti 1982
		15186	45	0.0511			Levinson 1966
Borna virus	NC_001607	8910	79	0.0292	0.0292	79	Danner 1979
Rabies virus	NC_001542	11932	10	0.2193	0.2193	10	Weiss 1986
Rauscher Murine Leukemia virus	NC_001819	8282	157	0.0147	0.00975	236	Kelloff 1970
		8282	480	0.0048			Lovinger 1975
Coronavirus (incl SARS)	NC_005147	30738	7	0.321	0.1106	21	Weiss 1986
	NC_004718	29751	226	0.01			Kariwa 2004
	NC_004718	29751	3046	0.000756			Darnell 2004
VEE	NC_001449	11438	55	0.04190	0.04190	55	Smirnov 1992
Avian Sarcoma virus	NC_008094	3166	155	0.0149	0.01047	220	Owada 1976
		3166	381	0.00604			Bister 1977
WEE	NC_003908	11484	54	0.043	0.04300	54	Dubinin 1975
Rous Sarcoma virus (RSV)	NC_001407	9392	720	0.0032	0.00640	360	Levinson 1966
		9392	240	0.0096			Golde 1961
Murine Norovirus	NC_008311	7382	76	0.0304	0.03040	76	Lee 2008
Semliki Forest virus	NC_003215	11442	25	0.0921	0.09210	25	Weiss 1986
Sindbis virus	NC_001547	11703	60	0.038645	0.03501	66	vonBrodorotti 1982
		11703	113	0.0203			Wang 2004
		11703	50	0.0461			Zavadova 1975
BLV	NC_001414	8419	1799	0.00128	0.00584	394	Shimizu 2004
		8419	221	0.01040			Guillemain 1981
HIV-1	NC_001802	9181	280	0.00822	0.00822	280	Yoshikura 1989
Avian Leukosis virus	NC_001408	7286	631	0.00365	0.00365	631	Levinson 1966
Measles	NC_001498	15894	22	0.10510	0.10510	22	DiStefano 1976
Moloney Murine Leukemia virus	NC_001501	8332	115	0.02	0.01148	201	Nomura 1972
		8332	370	0.00622			Guillemain 1981
		8332	280	0.00822			Yoshikura 1989
Friend Murine Leukemia virus	NC_001362	8323	320	0.0072	0.00720	320	Yoshikura 1971

Figure 2 shows a plot of equation (3) applied to ssRNA viruses that were averaged per species where more than one data set was available. There is a fairly definitive relationship across the entire potential dimerization range. The dimer proportionality constants used to fit equation (3) were: 1:0.1:6:6 (with the fourth constant being 4 for the triplets), or F_A=0.1, F_B=6, F_C=6.

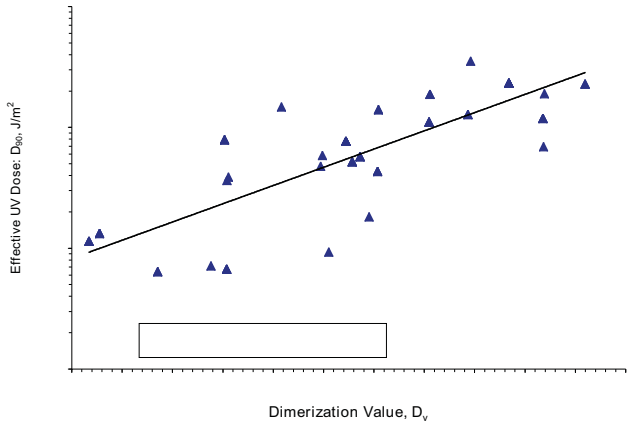

Figure 2: Plot of D_v versus effective D_{90} values for RNA animal viruses and bacteriophages – D_{90} is the effective dose because of correction for scatter. The line represents a curve fit (equation shown on graph), fit to 27 viruses, representing 70 data sets for UV irradiation tests in water.

It is curious to note that the slope of the curve in Figure 2 is positive, contrary to what intuition might suggest. That is, as the number of potential dimerization sequences in a genome increases, UV susceptibility also increases. It is for this reason that D_v is not referred to as a 'probability' value.

DNA Virus Model

Application of the model to double-stranded DNA (dsDNA) viruses requires some modifications to the ssRNA model. Double stranded DNA has a template strand and a complementary strand. The template strand will be accounted for in equation (6) but the complementary strand is not. However, a TT doublet in the complementary strand will be represented by an AA doublet on the template strand, and so counting base pairs can be done with the template strand alone, by interpreting the complementary bases. Incorporating the complementary strand bases produces the following equation:

$$D_v = \frac{\left[\sum(tt+aa)+F_a\sum(\overleftrightarrow{ct}+\overleftrightarrow{ag})+F_b\sum(cc+gg)+F_c\sum\left(\overleftrightarrow{YYU}+\overleftrightarrow{UUY}\right)\right]^{0.5}}{\sqrt[3]{bp^2}} \quad (7)$$

where $\overleftrightarrow{ct}$ = ct and tc (both ways, exclusive)

$\overleftrightarrow{ag}$ = ag and ga (both ways, exclusive)

$\overleftrightarrow{YYU}$ = YYU and UYY (both ways, exclusive)

$\overleftrightarrow{UUY}$ = YUU and YUU (both ways, exclusive)

F_a, F_b, F_c = proportionality constants

In addition to the doublets and triplets, it was found that the quadruplets onwards also contributed to the DNA model (which they did not for RNA viruses). The effect of the quadruplets, quintuplets, and sextuplets onwards can be characterized by a factor that accounts for hyperchromicity. A given oligonucleotide is hyperchromic if its overall absorbance is higher than the sum of its constituents molecules. Hyperchromicity occurs when multiple pyrimidines are stacked sequentially in clusters of three or more with the effect leveling off at about 8-10 pyrimidines in a row. Although not enough is known about the hyperchromic effect to quantify it exactly, a factor can be added to equation (7) to increase the probability of dimerization of any doublet or triplet whenever 3 or more pyrimidines are found in sequence (Kowalski et al 2009). The value of the factor is estimated by curve-fitting the data to obtain the best fit. In the present model the factor linearly increases the probability of dimerization for doublets and triplets based on how many adjacent pyrimidines are present in the genome, up to a value of 8 in a row. Each contribution can be defined as follows:

tt_n = # of tt doublets within n pyrimidines (template strand)

aa_n = # of aa doublets within n purines (complement strand)

tc_n = # of tc doublets within n pyrimidines (template strand)

ag_n = # of ag doublets within n purines (complement strand)

cc_n = # of cc doublets within n pyrimidines (template strand)

gg_n = # of gg doublets within n purines (complement strand)

UYY_n = # of UYY triplets within n pyrimidines (template strand)

UUY_n = # of UUY triplets within n purines (complement strand)

The equations for assigning the increase in probability due to hyperchromicity can then be written as follows:

$$tt_h = H\sum_{n=3}^{8}\left(n\cdot tt_n\right) \quad (8)$$

$$aa_h = H\sum_{n=3}^{8}\left(n\cdot aa_n\right) \quad (9)$$

$$tc_h = H\sum_{n=3}^{8}\left(n\cdot tc_n\right) \quad (10)$$

$$ag_h = H\sum_{n=3}^{8}\left(n\cdot ag_n\right) \quad (11)$$

$$cc_h = H\sum_{n=3}^{8}\left(n\cdot cc_n\right) \quad (12)$$

$$gg_h = H\sum_{n=3}^{8}\left(n\cdot gg_n\right) \quad (13)$$

$$UYY_h = H\sum_{n=3}^{8}\left(n\cdot UYY_n\right) \quad (14)$$

$$UUY_h = H\sum_{n=3}^{8}\left(n\cdot UUY_n\right) \quad (15)$$

where tt_h = hyperchromic multiplier, or increase in probability of dimerization from all multiple sequences of 3 to 8 pyrimidines. Similar for all other hyperchromic constants aah, tch, agh, cch, ggh, UYYh, and UUYh.

In equations (8) through (15), hyperchromic regions above 8 are neglected since such extended regions tend to be rare, and will be partly accounted for by these factors (i.e. any region of 8 pyrimidines in a row will contain a region of 8 in a row). Equation (5) is therefore re-written as follows:

$$D_v = \frac{\left[\begin{array}{c}\sum\left(tt+aa+tt_h+aa_h\right)+F_a\sum\left(\overleftrightarrow{ct}+\overleftrightarrow{ag}+\overleftrightarrow{ct}_h+\overleftrightarrow{ag}_h\right)+\\ F_b\sum\left(cc+gg+cc_h+gg_h\right)+F_c\sum\left(\overrightarrow{YYU}+\overrightarrow{UUY}+\overrightarrow{YYU}_h+\overrightarrow{UUY}_h\right)\end{array}\right]^{0.5}}{\sqrt[3]{bp^2}} \quad (16)$$

The proportionality constants represent the relative proportions of each type of dimer, which differ in RNA and DNA. Applying this model to DNA viruses produces the result shown in Figure 3. The dimer ratios for this curve fit were 1:0.2:40:18 (F_A=0.2, F_B=40, F_C=18), with a hyperchromicity factor H = 0.67 (meaning a multiplier of 1.67). The pattern of increasing D_{90} with increasing values of D_v seems fairly definitive. Table 4 lists 67 of the 77 virus data sets that were used in the ssRNA model, along with the average rate constants and the average D_{90} values representing 27 single-stranded RNA viruses. Viruses marked with an asterisk (*) indicate that additional data sets were used to compute the average rate constants – a maximum of 7 data sets were used per virus so as not to give undue weight to any virus. The remaining data sets are given in the References (Rainbow and Mak 1973 & 1970, Linden et al 2007, Wang et al 2004, Bossart et al 1978, Bourre et al 1989). Two additional data sets for T7 (MP and LP values) were accounted for in Table 4 (k=0.056 m^2/J and k=0.061 m^2/J) but not listed (Bohrerova et al 2008). The D_{90} values in Table 4 are uncorrected for UV scatter. No available data was omitted from Figure 3 and no outliers were excluded.

Table 4. *Rate Constants and D_{90} Values for DNA Viruses*

Virus	NCBI ID#	Genome bp	D_{90} J/m^2	UVGI k m^2/J	Avg k m^2/J	Avg D_{90} J/m^2	Source
Adenovirus Type 1	AC_000017	35997	299	0.0077	0.00714	322	Battiggelli 1993
			350	0.0066			Nwachuku 2005
Adenovirus Type 2*	AC_000007	35937	300	0.0077	0.00691	333	Shin 2005
			400	0.0058			Gerba 2002
Adenovirus Type 5*	AC_000008	35938	400	0.0058	0.00441	522	Durance 2005
			720	0.0032			Nwachuku 2005
Adenovirus Type 40	NC_001454	34214	546	0.0042	0.00422	546	Thurston-Enriquez 2003
Coliphage lambda	NC_001416	48502	57	0.0405	0.02953	78	Gurzadyan 1981
			70	0.0331			Harm 1961
			72	0.0320			Weigle 1953
			184	0.0125			Davidovich 1991
Simian virus 40*	NC_001669	5243	1599	0.0014	0.02768	83	Seemayer 1973
			1439	0.0016			Cornellis 1981
			1245	0.0019			Bockstahler 1977
			886	0.0026			Defendi 1967
			650	0.0035			Sarasin 1978
			443	0.0052			Aaronson 1970
			23	0.1004			Cornellis 1982
Hepatitis A virus	NC_001489	7478	40	0.0576	0.03513	66	Battigelli 1993
			45	0.0512			Wang 2004
			50	0.0461			Wiedenmann 1993
			92	0.0250			Wang 1995
			98	0.0234			Wilson 1992
			307	0.0075			Nuanualsuwan 2002
Herpes simplex virus Type 1	NC_001806	152261	100	0.0230	0.06262	37	Bockstahler 1976
			110	0.0209			Selsky 1978
			25	0.0933			Lytle 1971
			35	0.0654			Ross 1971
			21	0.1105			Albrecht 1974
Coliphage PRD1	NC_001421	14925	20	0.1150	0.115	20	Shin 2005
Vaccinia virus*	NC_006998	198350	7	0.3490	0.12454	18	Galasso 1965
			14	0.1604			Ross 1971
			18	0.1279			Klein 1994
			22	0.1050			Zavadova 1971
			28	0.0829			Rauth 1965
			715	0.0032			Davidovich 1991
			677	0.0034			Collier 1955
Coliphage T4	NC_000866	168900	7	0.3450	0.1709	13	Otaki 2003
			14	0.1685			Ross 1971
			15	0.1540			Harm 1968
			29	0.0800			Templeton 2006
			22	0.1070			Winkler 1962
B. subtilis phage SP	NC_004166	44010	100	0.0230	0.01742	132	Freeman 1987
			195	0.0118			Freeman 1987
Pseudorabies (PRV)	NC_005946	143461	34	0.0676	0.0676	34	Ross 1971
Murine Cytomegalovirus	NC_004065	230278	46	0.0500	0.05	46	Shanley 1982
HP1c1 phage	NC_001697	32355	40	0.0576	0.0576	40	Setlow 1972
Equine Herpes virus	NC_005946	150224	25	0.0921	0.0921	25	Weiss 1986
Frog virus 3	NC_005946	105903	25	0.0921	0.0921	25	Martin 1982
Coliphage T1	NC_005833	48836	6	0.3697	0.163	14	Hotz 1971
			38	0.0600			Harm 1968
			40	0.0580			Fluke 1949 (265 nm)
Coliphage T7	NC_001604	39937	95	0.0242	0.08192	25	Benzer 1952
			23	0.1000			Ronto 1992
			53	0.0432			Peak 1978 (B)
			11	0.2047			Peak 1978 (Bs-1)
Polyomavirus	NC_001699	5130	480	0.0048	0.0071	324	vander Eb 1967
			640	0.0036			Defendi 1967
			696	0.0033			Rauth 1965
			501	0.0046			Latarjet 1967
Mycobacterium phage D29	NC_001348	49136	16	0.1430	0.05623	41	David 1973
			324	0.0071			Sellers 1970 (D29)
			268	0.0086			Sellers 1970 (D29A)
Herpes simplex virus Type 2	NC_001798	154746	40	0.0576	0.06569	35	Wolff 1973
			41	0.0565			Ross 1971
			75	0.0307			Ryan 1986
			20	0.1180			Albrecht 1974

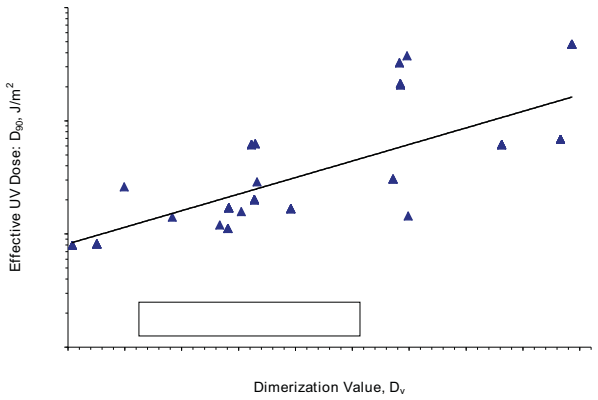

Figure 3: Plot of D_v versus effective UV dose for DNA viruses – the D_{90} is the effective dose because it has been corrected for UV scattering. The line represents a curve fit (equation shown on graph). A total of 77 data sets were used, weighted in the curve fit of the 22 viruses.

Table 5 compares the published estimates of the relative proportions of the various dimer types with the constants used in the previous models. The factors shown in the table are the three constants in equations (7) and (16). The best fit constants are those that were used in the model in the previous Figures. The zero values assumed for the constants that were not given by the indicated sources did not have any great influence of the R^2 value. The hyperchromicity factor was zero for all RNA models, and kept at 0.67 for all DNA models. The results for the DNA model are shown with and without corrections for UV scattering, which make about an 12% difference in the DNA model, but had only a 1% difference on the RNA model, as would be expected from their size. Hyperchromicity had no effect on the RNA model but produced a 1% improvement in the DNA model.

Dimer	Dimer Ratio	Factor	Setlow 1968	Meistrich 1970	Lamola 1973	Unrau 1973	Patrick 1977	Best Fit RNA	Best Fit DNA
TT	1	1	1	1	1	1	1	1	1
CT	CT/TT	F_A	0.25	0.8	0.8	0.5	1	0.1	0.05
CC	CC/TT	F_B	0.13	0.2	0.2	0.5	1	6	40
UYY	UYY/TT	F_C	0	0	0	0	0	6	18
RNA Model R^2 (NS)			61%	60%	60%	64%	62%	66%	-
RNA Model R^2			59%	61%	61%	64%	62%	67%	-
Hyperchromicity		H	0.67	0.67	0.67	0.67	0.67	0	0.67
DNA Model R^2 (NS)			33%	33%	33%	36%	39%	-	50%
DNA Model R^2 (NH)			41%	44%	44%	48%	51%	-	61%
DNA Model R^2			43%	46%	46%	50%	53%	-	62%

(NH): No hyperchromicity. (NS): UV scattering not included.

Table 5: *Comparison of Dimerization Proportionality Constants*

CONCLUSIONS

A mathematical model has been presented for the prediction of UV susceptibility of RNA and DNA viruses based on base-counting of potential dimers in the virus genomes. The results correlate well with available data on UV rate constants. This model has been used to estimate the UV rate constants for a range of pathogenic animal viruses and bioweapon agents for which complete genomes were available from the NCBI database and Table 6 summarizes these predictions. Minimum and maximum D_{90} values are listed that are within the confidence intervals (CIs) of 86% for DNA viruses and 93% for RNA viruses. These CIs represent only the intervals of the data as summarized and do not include any uncertainty in the original 147 data sets, most of which included no error analysis. By establishing a theoretical basis for the UV susceptibility of viruses in water, it becomes possible to link them to airborne rate constants – water-based rate constants represent a limit towards which airborne rate constants converge in high humidity (Peccia et al 2001). For additional information on genomic modeling see Kowalski et al (2009) and Kowalski (2009).

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Table 6. *Predicted UV Rate Constants and D_{90} Values*

Virus	Type	NCBI #s	Dia. μm	Genome bp	Dimer Prob D_v	UV k m^2/J	UV Dose D_{90}, J/m^2		
							Mean	Min	Max
Camelpox	DNA	NC_003391	0.307	205719	0.3968	0.1280	18	9.6	40
Canine Distemper	DNA	NC_001921	0.173	15690	0.6958	0.0182	126	38	442
Chikungunya	RNA	NC_004162	0.06	11826	0.2161	0.0763	30	9.7	66
Crimean-Congo	RNA	NC_005300,01,02	0.09	19146	0.1947	0.1261	18	6.6	37
Dengue Fever Type 1	RNA	NC_001477	0.045	10735	0.2117	0.0996	23	7.5	49
Dengue Fever Type 2	RNA	NC_001474	0.045	10723	0.2080	0.1146	20	6.9	44
Dengue Fever Type 3	RNA	NC_001475	0.045	10707	0.2091	0.1113	21	7.2	45
Dengue Fever Type 4	RNA	NC_002640	0.045	10649	0.2125	0.0946	24	7.7	51
Ebola (Reston)	RNA	NC_004161	0.09	18891	0.2043	0.0957	24	8.3	51
Ebola (Sudan)	RNA	NC_006432	0.09	18875	0.2066	0.0867	27	8.8	53
Ebola (Zaire)	RNA	NC_002549	0.09	18959	0.2035	0.0991	23	8.3	50
EEE	RNA	NC_003899	0.062	11675	0.2222	0.0613	38	12	83
Fowl Adenovirus A	DNA	NC_001720	0.08	43804	0.6479	0.0349	66	33	220
Fowlpox	DNA	NC_002188	0.307	288539	0.3652	0.1564	15	7.7	30
Goatpox	DNA	NC_004003	0.307	149599	0.3987	0.1232	19	10	40
Hantaan	RNA	NC_005218,19,22	0.095	11845	0.2086	0.0811	28	9.9	63
Hepatitis C	DNA	NC_009827	0.06	9628	0.8542	0.0099	233	110	1097
Herpesvirus Type 4	DNA	NC_009334	0.122	172764	0.5879	0.0436	53	25	157
Herpesvirus Type 6A	DNA	NC_001664	0.1	159322	0.4626	0.1103	21	11	50
Herpesvirus Type 7	DNA	NC_001716	0.155	153080	0.4459	0.1024	22	12	49
Japanese Encephalitis	RNA	NC_001437	0.045	10976	0.2163	0.0860	27	8.9	61
Junin	RNA	NC_005080,81	0.12	10525	0.2304	0.0341	68	21	154
Lassa	RNA	NC_004296,97	0.12	10681	0.2294	0.0372	62	20	107
LCM	RNA	NC_004291,94	0.126	10056	0.2226	0.0430	54	17	118
Machupo	RNA	NC_005079,78	0.11	10635	0.2326	0.0334	69	22	156
Marburg	RNA	NC_001608	0.039	19111	0.1999	0.1654	14	5.0	30
Monkeypox	DNA	NC_003310	0.307	196858	0.3998	0.1232	19	10	40
Mousepox	DNA	NC_004105	0.307	209771	0.3951	0.1247	18	9.8	40
Mumps	RNA	NC_002200	0.245	15384	0.2133	0.0486	47	15	97
Myxoma	DNA	NC_001132	0.25	161766	0.4451	0.0924	25	13	54
Norwalk	RNA	NC_001959	0.032	7654	0.2416	0.0410	56	14	132
Papillomavirus	DNA	NC_001691	0.055	7184	0.7302	0.0236	98	45	369
Parainfluenza Type 1	RNA	NC_003461	0.194	15600	0.1961	0.0968	24	8.6	50
Respiratory Syncytial	RNA	NC_001803	0.19	15225	0.2006	0.0823	28	9.7	58
Rhinovirus B	RNA	NC_001490	0.023	7212	0.2355	0.0526	44	12	99
Rhinovirus C	RNA	NC_009996	0.023	7099	0.2428	0.0417	55	15	125
Rubella	RNA	NC_001545	0.061	9755	0.2634	0.0152	152	37	345
Sendai	RNA	NC_001522	0.194	15384	0.2040	0.0740	31	11	66
Smallpox	DNA	NC_001611	0.307	185578	0.4041	0.1202	19	10	42
Turkey Adenovirus A	DNA	NC_001958	0.08	26263	0.6030	0.0473	49	24	148
Usutu	RNA	NC_006551	0.051	11066	0.2206	0.0693	33	10	73
Yellow Fever	RNA	NC_002031	0.045	10862	0.2151	0.0860	27	8.5	56

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