Electron breakthrough for COVID-19 delta variant

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COVID-19 is extremely dangerous and as of 15-Apr-2021 it has killed more than half a million people in the US and several million people worldwide in the past 18 months. A new variant called delta (31-May-2021) by the World Health Organization is now creating a medical crisis in parts of the US and around the world. The delta mutation of the spike protein is substantially more contagious. The secret to the deadly nature of COVID-19 is in the amino acid sequence of the spike protein, how it contacts the host molecule it infects and how fast it replicates.
About 30 – 100 spike proteins protrude from the surface of each virus particle. The particle has a reported diameter of about 0.1 microns in the dry state. The diameter increases when the particle picks up water and other substances. The particle needs to pick up water for the ion channels to function and for virus replication. Ion channel functioning needs a 3-4 nm lipid bilayer membrane. Each spike protein has a sequence of 1273 amino acid residues.[1]

A 3-D electron-gated structure for the spike protein ion channel was developed and is presented in Fig. 21A and Fig. 21B.
The higher contagion rate of the delta variant of the COVID-19 virus is predicted by the ion channel model. Reduced tunneling distance and time constants in the delta variant result in a 3-fold increase in the replication rate for delta. This causes an exponential increase in the total number of particles produced at a time (interval) of t hours. The graph for the delta time constant (Fig. 21E) shows 10^{23} particles produced at t =10 hours with η =20% replication efficiency. For the COVID-19 time constant (Fig, 21D) only 10^{7} particles are produced at t =10 hours and η =20% replication efficiency.
Virus particles disabled by a vaccine would have a reduced replication efficiency.
This study also reveals the mutation in the structure of the virus which is responsible for the dramatic increase in the delta variant contageousness.
The structure gives a map showing locations for reported mutations, including the delta variant.
Research published in the book *Electron-gated ion channels*[2] shows how tunneling electrons control the gates and time constants in Na, K, and Ca ion channels. In 2019-2020 a new 3-D modeling technique was introduced on my website (www.biokinetix.org) that gives structures and/or alignments for Na, K, Ca ion channels based on the amplified electron tunneling and gating model published in the book.
Amplified electron tunneling and gating offers a giant leap forward for understanding ion channels and diseases.
The spike protein structure presented here reveals for the first time why the delta mutation in COVID-19 replicates the virus faster, making delta more contagious. This is only possible because of research published in the book *Electron-gated ion channels* (2005).[2]

Findings for the spike protein structure.
1. There are 4 domains.
2. Structure is similar to Cav1.2, L-type calcium channel structure.
3. U1 gating cavities start with E (Glutamate) as for calcium channels.
4. Distance between U1 and U2 gating cavities is 4-residues less than for Cav1.2.
5. There are 24 α-helices labeled S1,S2,S3,S4,S5,S6 in 4 domains D1,D2,D3,D4, however, S1 and S2 on D2 and D4 have binding cavities due to fewer residues.

A strong binding force to the host makes COVID-19 deadly.
A strong binding force could result from a long contact distance with D4 residues on S4, S5 and S3. The missing S1 and S2 α-helix residues on D4 and D2 (shown in Yellow) are the most striking observation for the electron-gated structure. Reported mutations for the B.1.1.7 Spike are shown on the ion channel sequence map (Fig. 21A).

The faster replicating delta variant needs the T478K mutation plus K417.
The mutation T478K places a lysine residue in alignment with the U2B gating cavity. Lysine residue K417 on D2-S3 has a NH3 tunneling site labeled q_L. This site reduces the electron tunneling time constant (q_5-q_{F12}) from 15 min to about 20 s (0.0055 h). Oscillating electron tunneling between q_5 and q_{F12} produces gating pulses that can substantially increase the number of particles produced as shown in Fig. 21E.

Fig. 21A. COVID-19 spike protein, Electron-gated ion channel structure & reported mutations

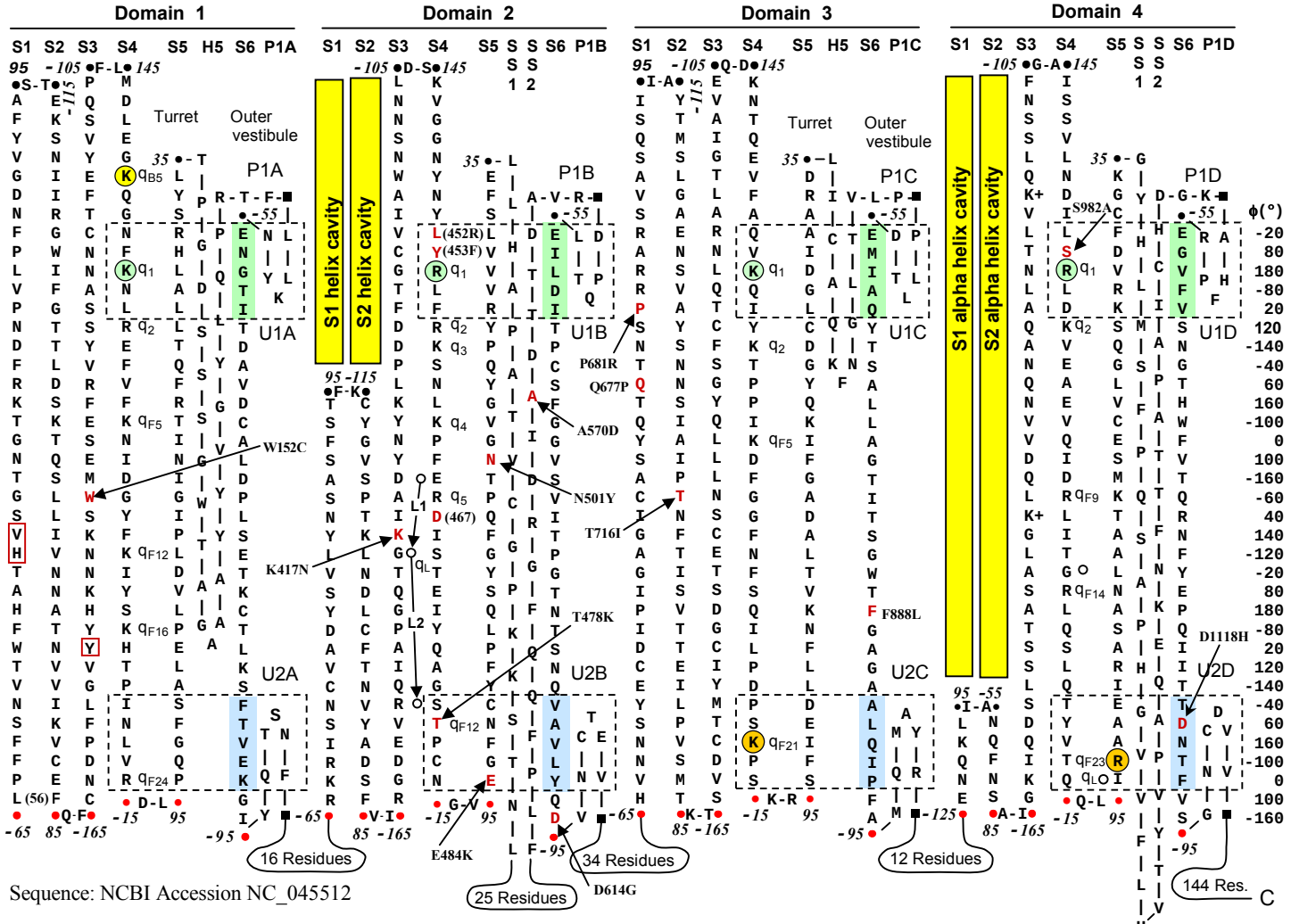
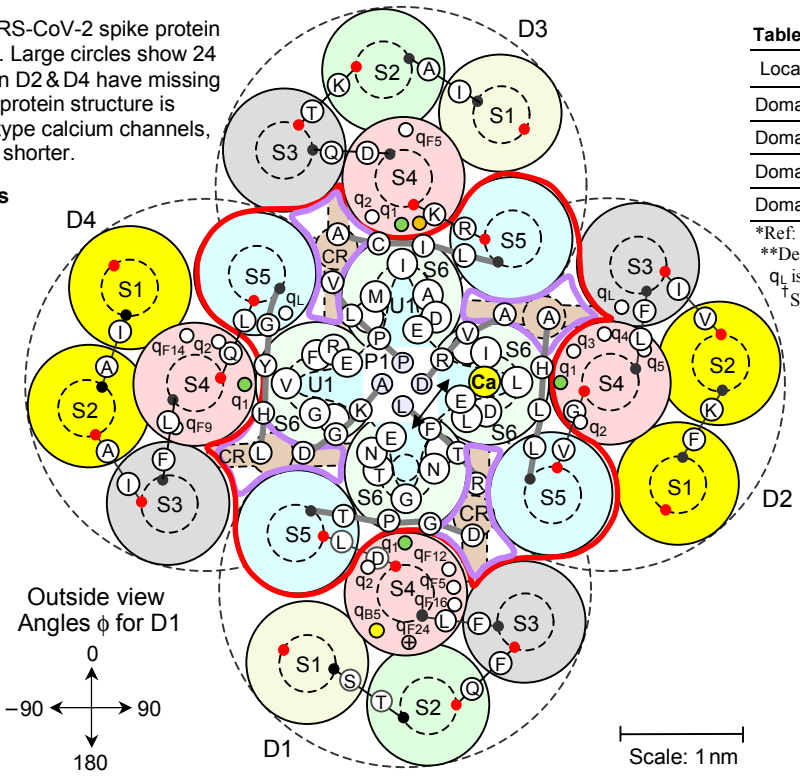


Fig. 21B.

Cross section of SARS-CoV-2 spike protein viewed from outside. Large circles show 24 α-helices. S1 & S2 on D2 & D4 have missing residues. The spike protein structure is similar to Cav1.2 L-type calcium channels, but S6 is 4-residues shorter.



Reported Mutations

Delta variant
D2 S4 T478K, L452R
D2 S5 E484K

D1 S3 W152C US
D2 S3 K417N SA
D2 S3 K417T J B
D2 S4 L452R US
D2 S4 Y453F D
D2 S4 T478K UK I US
D2 S5 E484K SA N B J I
D2 S5 N501Y UK SA J B
D2 S6- A570D
D2 S6 D614G E C
D3 S1 Q677P US
D3 S1 P681R UK N
D3 S2 T716I
D3 S6 F888L UK N
D4 S4 S982A
D4 S6 D1118H

US: UNITED STATES
UK: UNITED KINGDOM
SA: SOUTH AFRICA
N: NIGERIA
B: BRAZIL
D: DENMARK
E: EUROPE
J: JAPAN
C: CHINA
I: INDIA

Table 21-1. Electron tunneling time constants

Location	Sites	Residues	Distance*	Time*
Domain 1	q_{F16} -q_{F24} †	8	13.0 Å	1 s
Domain 2	q_5 -q_{F12} **	12 & q_L	19.2 Å & q_L	20 s
Domain 3	q_{F5} -q_{F21}	16	25.2 Å	hrs-days
Domain 4	q_{F9} -q_{F23}	9+2=11	16.5 Å	1 min

*Ref: Ch. 8 and Table 8-1, Electron-gated ion channels (2005).
**Delta variant mutation T478K increases replication rate.
q_L is lateral tunneling site not on S4, but on D2-S3 and D4-S5.
† Site q_{F24} may be charged and not an electron tunneling site.

- H5 residue chain
- Periphery of outer vestibule
- Intra-helix crevices (IHC)
- NH_3 Arg/Lys tunneling site
- Arg/Lys charged or neutral
- Glu/Asp charged or neutral
- Activation control site
- Inactivation control site
- α-helix end residue terminal
- (CR) Crevice Residues

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Fig. 21C. Total number with x replications

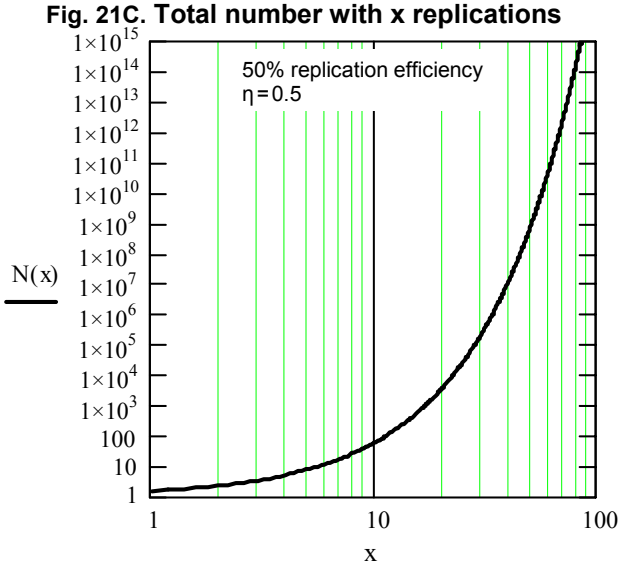

Fig. 21D. Total number of particles at time t

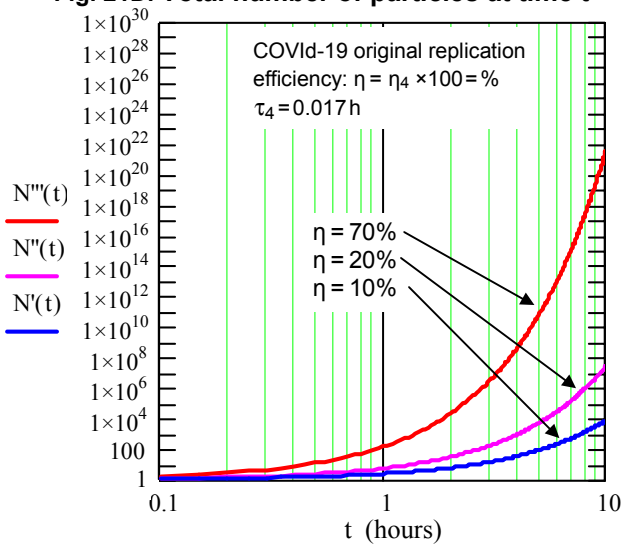

Fig. 21E. Total number of particles at time t

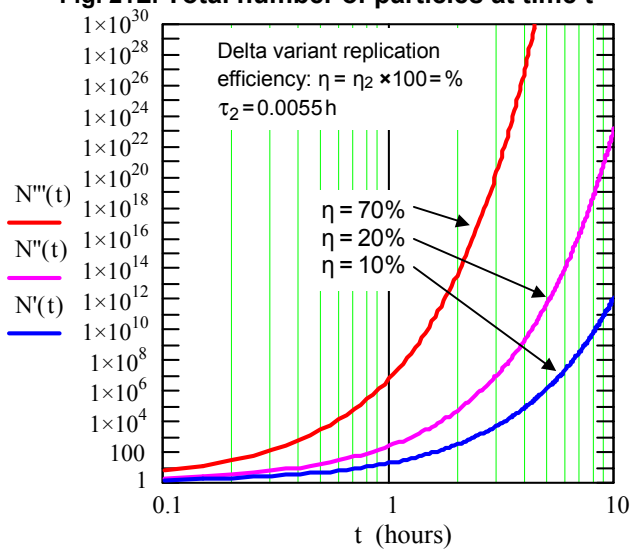

Table 21-2. Equations for replication calculations

N(x) is total after x replications	$N(x) := (1+\eta)^{x}$	(21.1)
Original Domain 4	$N_4(t) := (1+\eta_4)^{\frac{t}{2\cdot\pi\cdot\tau_4}}$	(21.2)
Delta variant Domain 2	$N_2(t) := (1+\eta_2)^{\frac{t}{2\cdot\pi\cdot\tau_2}}$	(21.3)

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Figs. 21C,D,E. Replication graphs for COVID-19 and delta variant shows delta is a faster replicator. The delta variant of COVID-19 replicates faster than the original virus, but what is the mechanism for this? The structure in Fig. 21A,B. provides a map showing the mutation(s) that make the delta variant replication faster.

A key finding from the structure is a lysine (K) lateral tunneling site labeled q_L on D2-S3. This amino acid reduces the tunneling distance to q_{F12}, which is mutated to lysine (K) for delta. The estimated electron tunneling time constant is 20 s (0.0055 h). Here, the electron tunnels back and forth between q_5 and q_{F12} producing gating pulses causing a pulsing energy barrier at U2B. The other oscillating site is an arginine lateral site q_L on D4-S5, which produces pulses at a lower frequency with a time constant of 1 min (0.017 h). Tunneling time constants are from Table 21-1. The oscillators function like the calcium oscillator described in Ch. 8 and Fig. 8-5 in the book *Electron-gated ion channels* (2005).

The q_L lysine site on D2-S3 has an angle $\phi = -60°$ placing it near q_5 as shown in Fig. 21B. Without the S3 q_L site the time constant is 15 min and fast replication for the delta variant would not be possible. The S3 q_L tunneling bypass is similar to the Kv1.2 bypass on S3 that reduces tunneling time from 2 h to 1 s. The Kv 2.1 subunit structure is shown in Fig. 9 on biokinetix.org.

Cascaded gating cavities combine pulses produced at inactivation control sites.
Each spike protein has 4 inactivation gate cavities labeled U1A to U1D. When an ion current flows the Ions must sequentially pass through all 4 cavities. When an electron tunnels to a control site it creates an energy barrier at the adjacent gating cavity. This stops (reduces by 20-100 fold) ion channel current. For the delta variant, the inactivation system can be treated as 3 switches in series. To have an ion current all switches must be closed. The electron controlling switch opening is tunneling (oscillating) to and from the control site at a frequency determined by the time constant for electron tunneling. The tunneling oscillations are driven by amplifying arginine or lysine NH3 sites. This was developed in Ch. 2 and Ch. 3 in the book Electron-gated ion channels (2005).[2]

The COVID-19 delta variant has three channels with inactivation pulsing.
1. The original spike protein uses q_{F23} on D4-S5 to produce energy barrier pulsing on U2D.

2. The delta variant channel is created by the mutation T478K. This places a lysine residue on D2-S4 near the U2B gating cavity. The S3 site K417 is also required to reduce the time constant.
A mutation K417N has been called “Delta plus”.[3] Removing this lysine tunneling site increases the D2 channel time constant from 20 s to 15 min and slows replication to that of the original virus.

3. The spike protein-tunneling site q_{F21} on D3-S4 has a time constant of hours to a day or more. When the electron tunnels to q_{F21} it goes into sleep mode creating an energy barrier at U2C that attenuates ion channel current. Replication is likely stopped or reduced during sleep mode.
Along with sleep mode the virus may have a circadian rhythm controlled by the time constant for q_{F21}.
The efficiency η controls the virus replication rate for the curves in Fig. 21D and Fig. 21E.
The curve for $N_2(t)$ shows a rapid build up to 10^{27} virus particles in 4 hours with efficiency $\eta = 0.7$.
Vaccine binding near the Domain 2, S1 & S3, cavities should lower the value for η and $N_2(t)$ curve.

A Bat SARS-like coronavirus also has three channels with inactivation pulsing.
An electron-gated ion channel structure was developed for the spike protein in a BAT SARS-like Coronavirus. The Bat structure (Fig. 22A,B.) also shows three channels with inactivation pulsing and is included here for comparison. It has the same time constants as the COVID-19 delta variant.
The spike protein for both ion channel models has a cylindrical shape; 6nm in diameter by 6nm high. The height is given in Fig. 21A by the number of S3 amino acids in one α-helix crossing times the individual rise distance of 0.15nm, (40×0.15nm =6nm). The diameter as shown in Fig. 21B is 6nm. The 0.7 nm 2-residue cross links hold the adjacent α-helices together and determine the overall diameter. The links are between black dots on the outside and red dots on the inside.

References

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   Authors: Fan Wu, Su Zhao, Bin Yu, Yan-Mei Chen, Wen Wang, Zhi-Gang Song, Yi Hu, et al.
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   Authors: Dan Hu, Changqiang Zhu, Lele Ai, Ting He, Yi Wang, Fuqiang Ye, Lu Yang, Chenxi Ding, Xuhui Zhu, et al.

Fig. 22A. Spike protein [Bat SARS-like coronavirus] Electron-gated ion channel structure

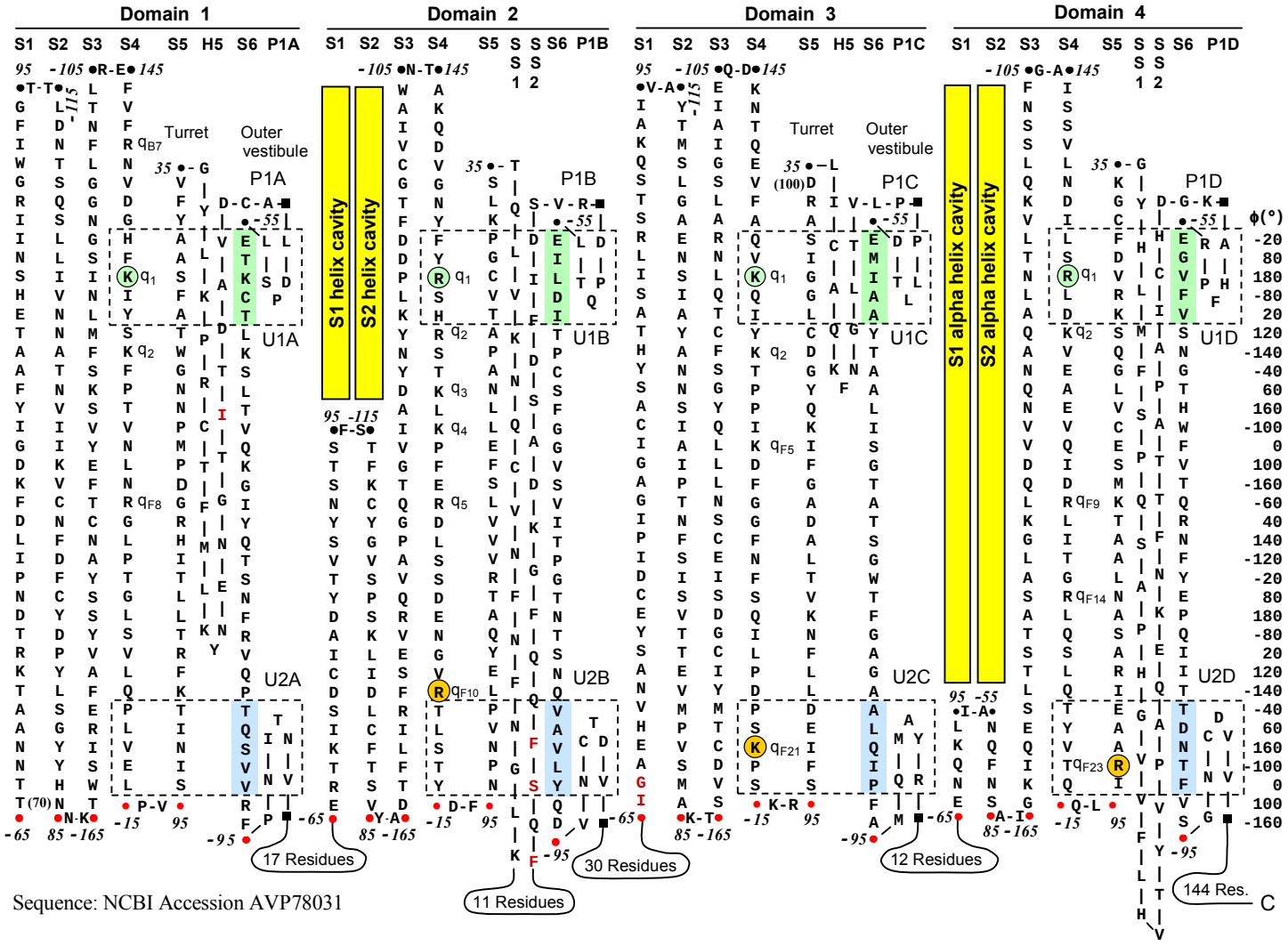

Fig. 22B.

Cross section of BAT spike protein viewed from outside. Large circles show 24 α-helices. S1 & S2 on D2 & D4 have missing residues. The protein structure is similar to Cav1.2, L-type calcium channels, but S6 is 4-residues shorter.

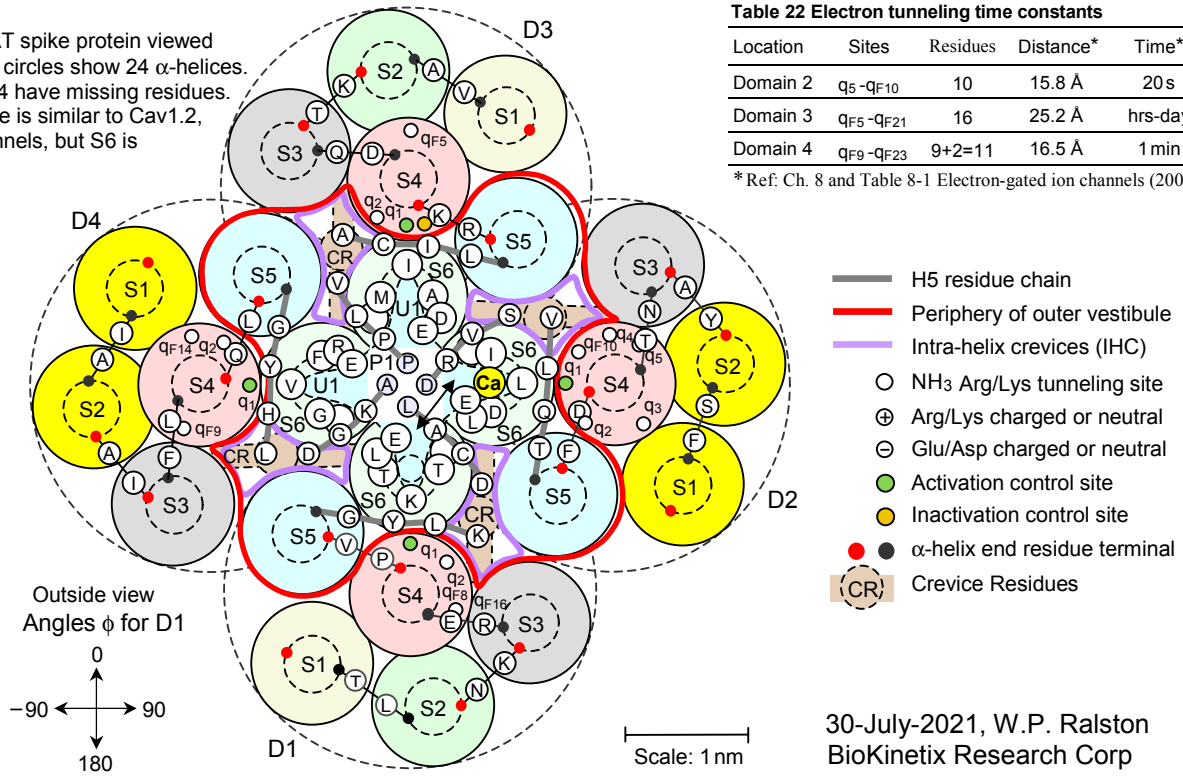

Table 22 Electron tunneling time constants

Location	Sites	Residues	Distance*	Time*
Domain 2	q_5 -q_{F10}	10	15.8 Å	20 s
Domain 3	q_{F5} -q_{F21}	16	25.2 Å	hrs-day
Domain 4	q_{F9} -q_{F23}	9+2=11	16.5 Å	1 min

*Ref: Ch. 8 and Table 8-1 Electron-gated ion channels (2005)

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