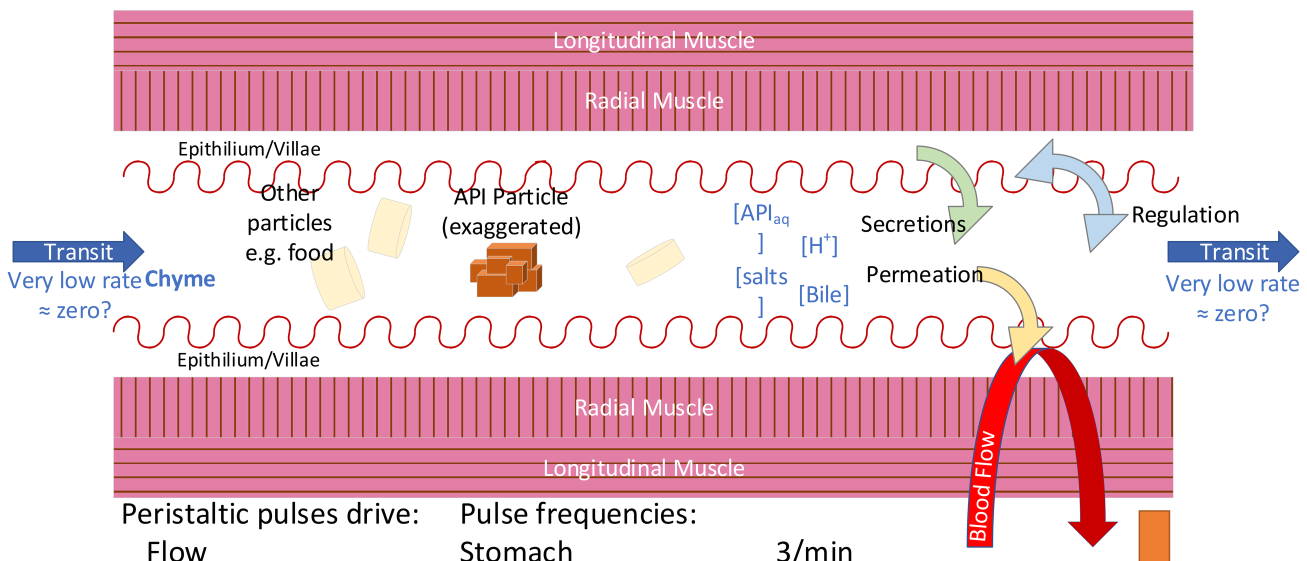
Understanding Dissolution Rate

ADVANCED DIGITAL DESIGN OF PHARMACEUTICAL THERAPEUTICS

Scale: GI Tract (Including Stomach)

Between Peristaltic Pulses



Peristaltic pulses drive:
- Flow
- Shear
- Mixing

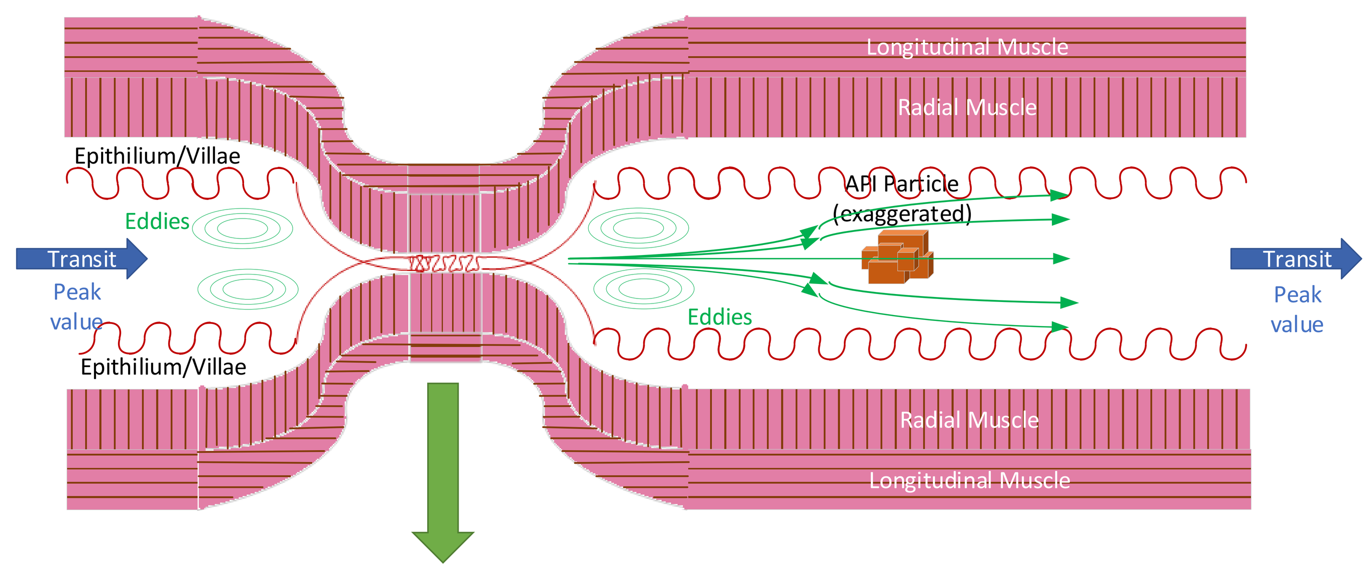
Pulse frequencies:

Stomach	3/min
Duodenum	12/min
Ileum	9/min
Large intestine	2/hour

Transformation	Entities	Properties	Physics	Parameters	Order of Magnitude
Dissolution	All dissolved species All soluble solid species Chyme	[Solutes] Solubility	Diffusion	Diffusion coefficients	Minutes
Permeation	All dissolved species Chyme Membrane Blood	[Solutes]	Osmosis	Osmotic pressure	Seconds

Pulse Cycle

During Peristaltic Pulses

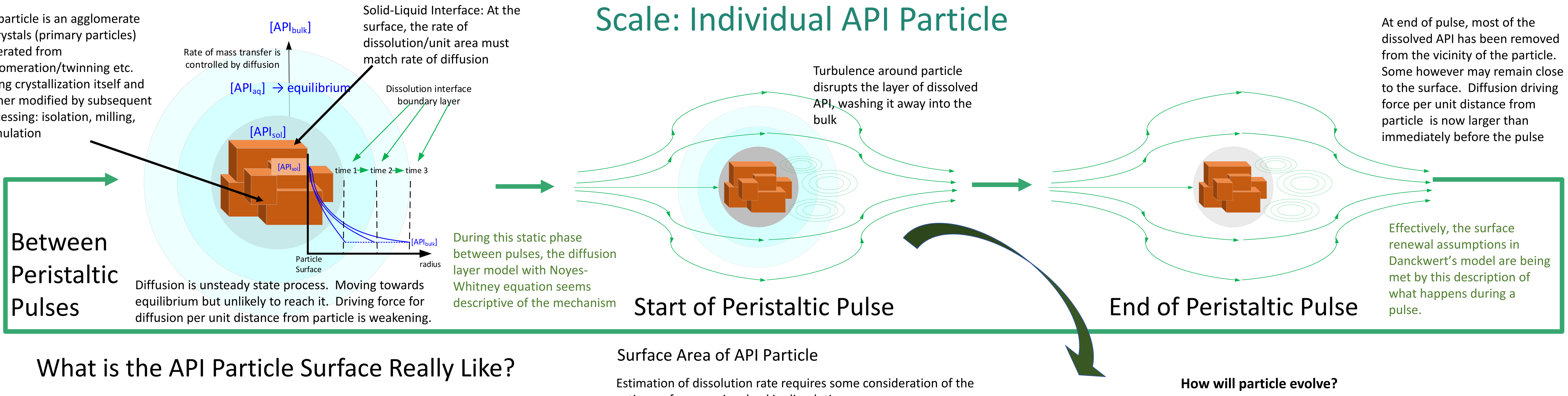


Transformation	Entities	Properties	Physics	Parameters	Order of Magnitude
Mixing	All dissolved species All solid species Chyme	[all species] Viscosity Density Particle size	Flow profile Turbulence	Reynolds number	Seconds every 10's seconds

Scale: Individual API Particle

API particle is an agglomerate of crystals (primary particles) generated from agglomeration/twinning etc. during crystallization itself and further modified by subsequent processing: isolation, milling, formulation

Solid-Liquid Interface: At the surface, the rate of dissolution/unit area must match rate of diffusion



Diffusion is unsteady state process. Moving towards equilibrium but unlikely to reach it. Driving force for diffusion per unit distance from particle is weakening.

During this static phase between pulses, the diffusion layer model with Noyes-Whitney equation seems descriptive of the mechanism

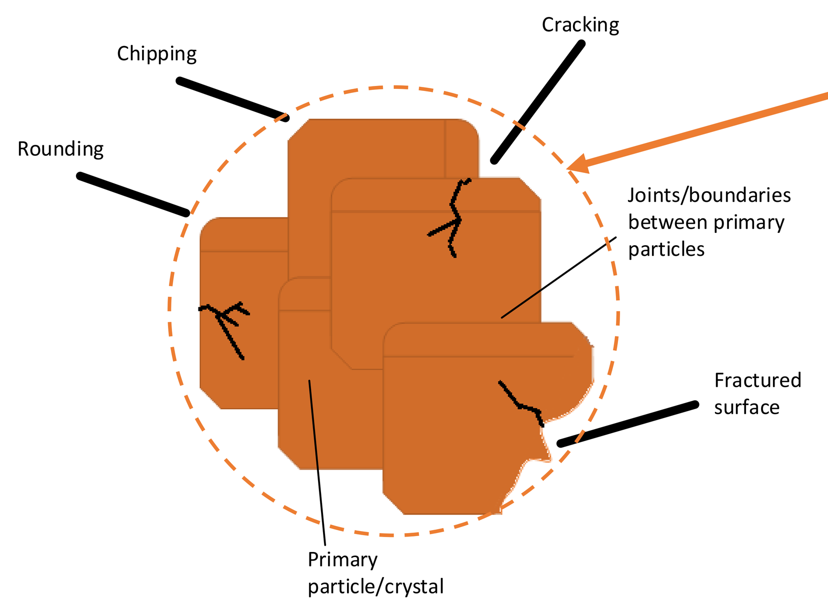
Turbulence around particle disrupts the layer of dissolved API, washing it away into the bulk

At end of pulse, most of the dissolved API has been removed from the vicinity of the particle. Some however may remain close to the surface. Diffusion driving force per unit distance from particle is now larger than immediately before the pulse

Effectively, the surface renewal assumptions in Danckwert's model are being met by this description of what happens during a pulse.

What is the API Particle Surface Really Like?

Does the existence/prevalence of these different features significantly modify the dissolution rate
- On average across all particles?
- From particle to particle?
- Surface location to surface location?



Surface Area of API Particle

Estimation of dissolution rate requires some consideration of the active surface area involved in dissolution.

Models tend to assume spherical particles

Which definition for an equivalent diameter sphere is the best representation of the complicated surface of a real particle?

Is the Sauter Mean diameter the right parameter for dissolution?

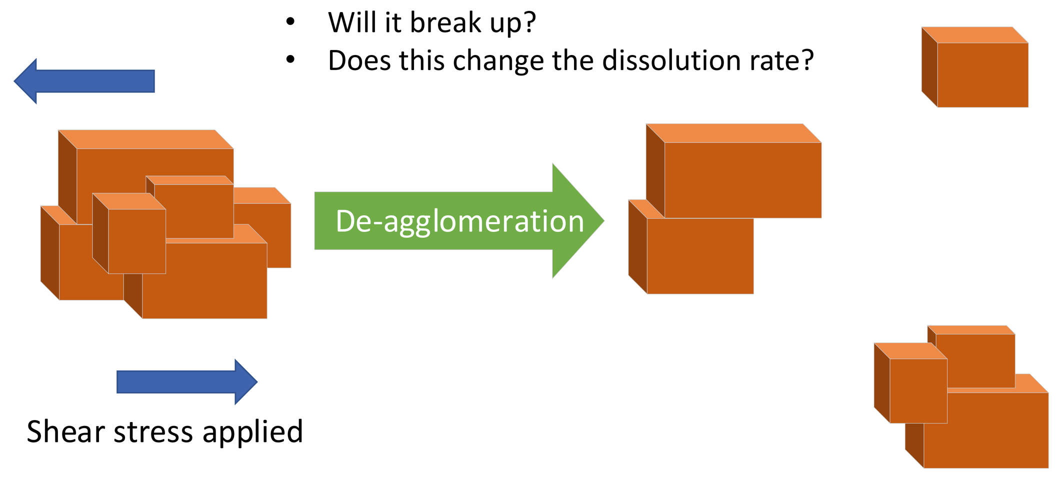
$$Sauter\ mean, d_{32} = \frac{d_v^3}{d_s^2}$$

$$Surface\ dia, d_s = \sqrt{\frac{A_p}{\pi}}$$

$$Volume\ dia, d_v = \left(\frac{6V_p}{\pi}\right)^{\frac{1}{3}}$$

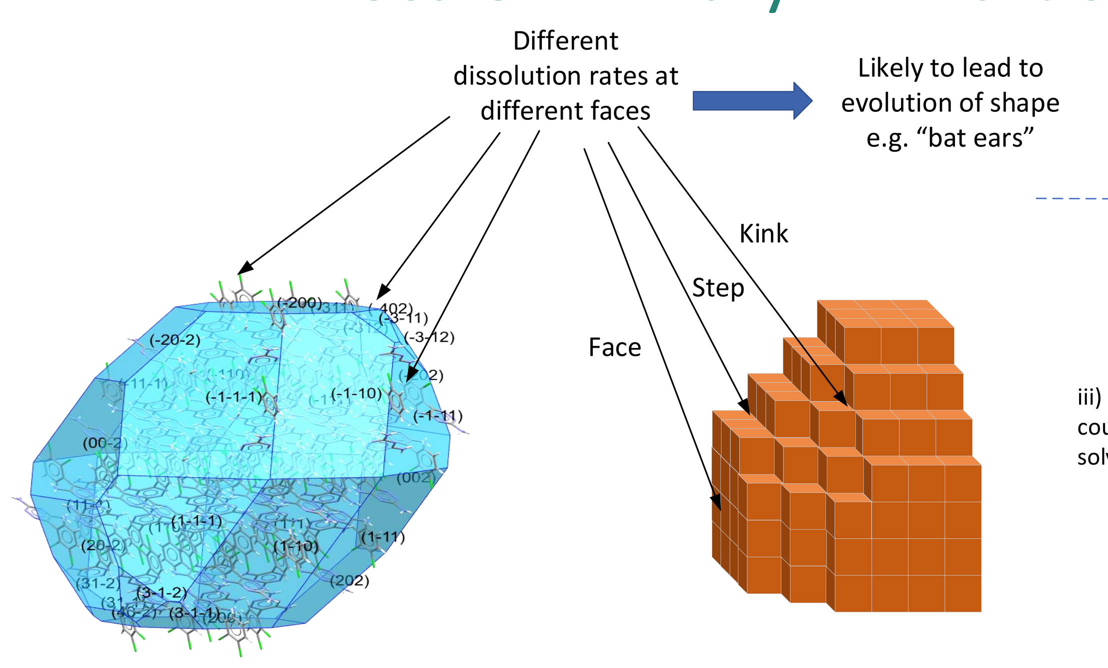
If the Sauter mean is used to describe the particle size, it can be probably used to allow a relatively simple comparison relative dissolution rates.

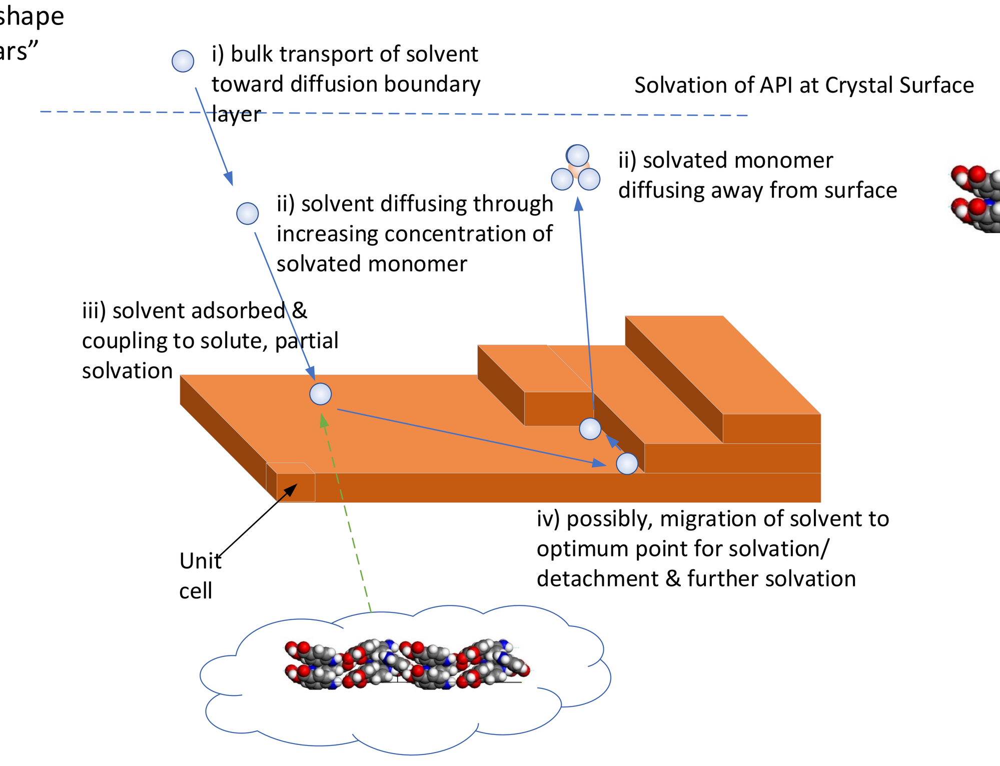
How will particle evolve?
- Will it break up?
- Does this change the dissolution rate?



Gradual Break-up of API Agglomerate into Primary Particles

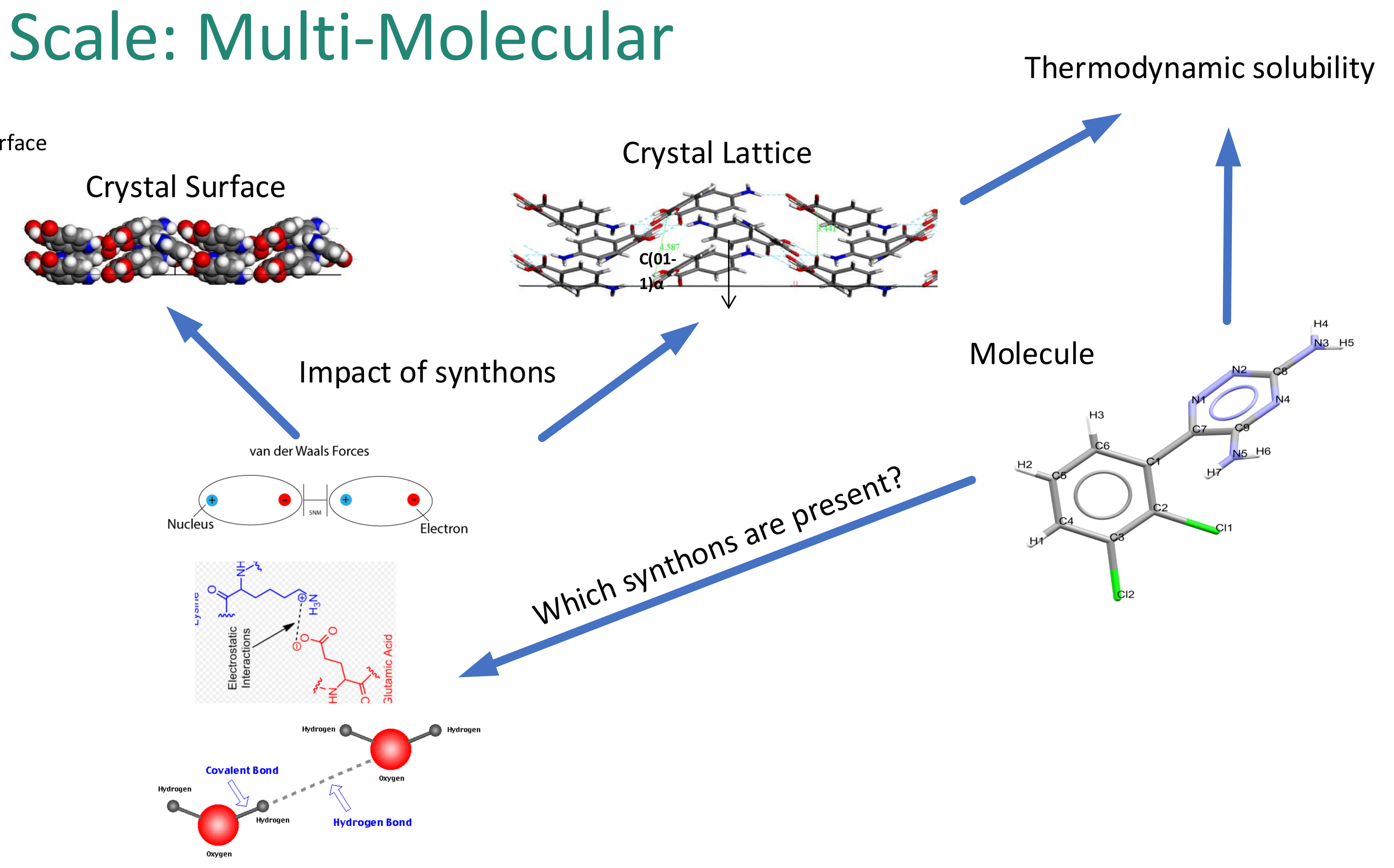
Scale: Primary API Particle Surfaces





Solvation of API at Crystal Surface

Scale: Multi-Molecular



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