In silico modelling: Subcutaneous Bioavailability of mAbs

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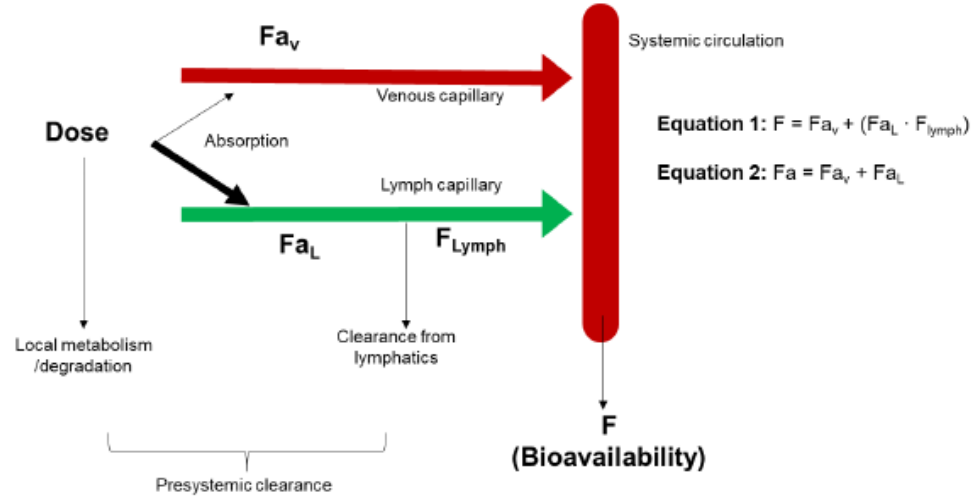
SC In silico modelling

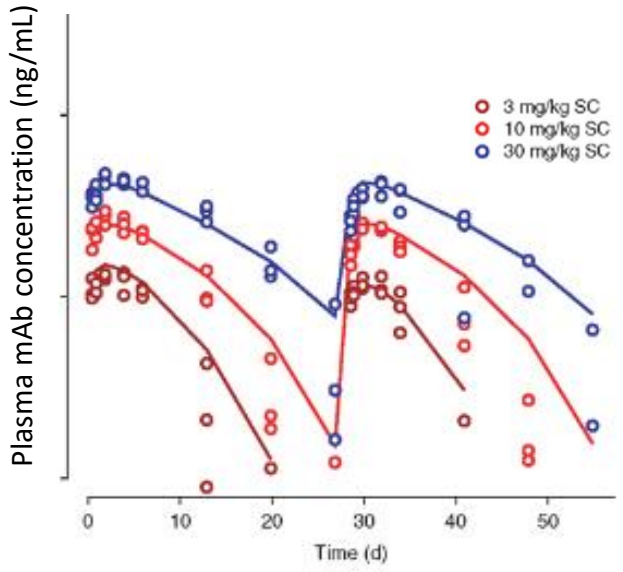
- In silico absorption modelling is successfully used in oral formulation development for compound selection, formulation design, specification setting and sometimes even in lieu of clinical bioequivalence studies
- Compared to oral, SC models are less well established, and are acknowledged as complex due to multiple, interrelated nonlinear pathways
- Empirical and mechanistic models have been developed
- None can predict SC mAb bioavailability bottom-up
- Aim to predict or understand factors affecting rate and extent of absorption and impact on PK profile
- Knowledge gaps/opportunities to improve the models have been proposed

Schematic representing SC Bioavailability (F)



F, bioavailability; Fa, fraction absorbed; Fa_L, fraction absorbed via lymph; Fa_v, fraction absorbed via venous capillary; F_{Lymph}, fraction escaping lymphatic clearance.

Example mAb SC PK profile



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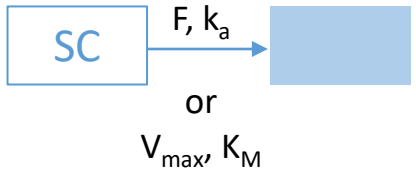
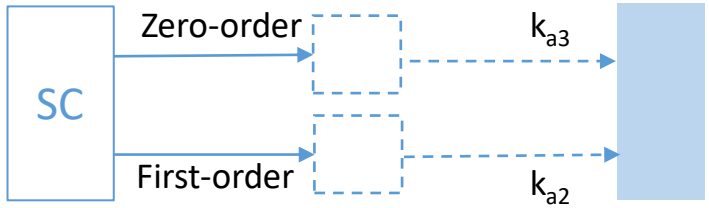
Empirical Models

- Empirical models are:
  - Developed from studies measuring plasma/serum concentration
  - Not physiological
  - Parameterised by data fitting
  - Useful to describe observed behaviour and extrapolation to different dose/frequency

Single-pathway model



Dual-pathway model

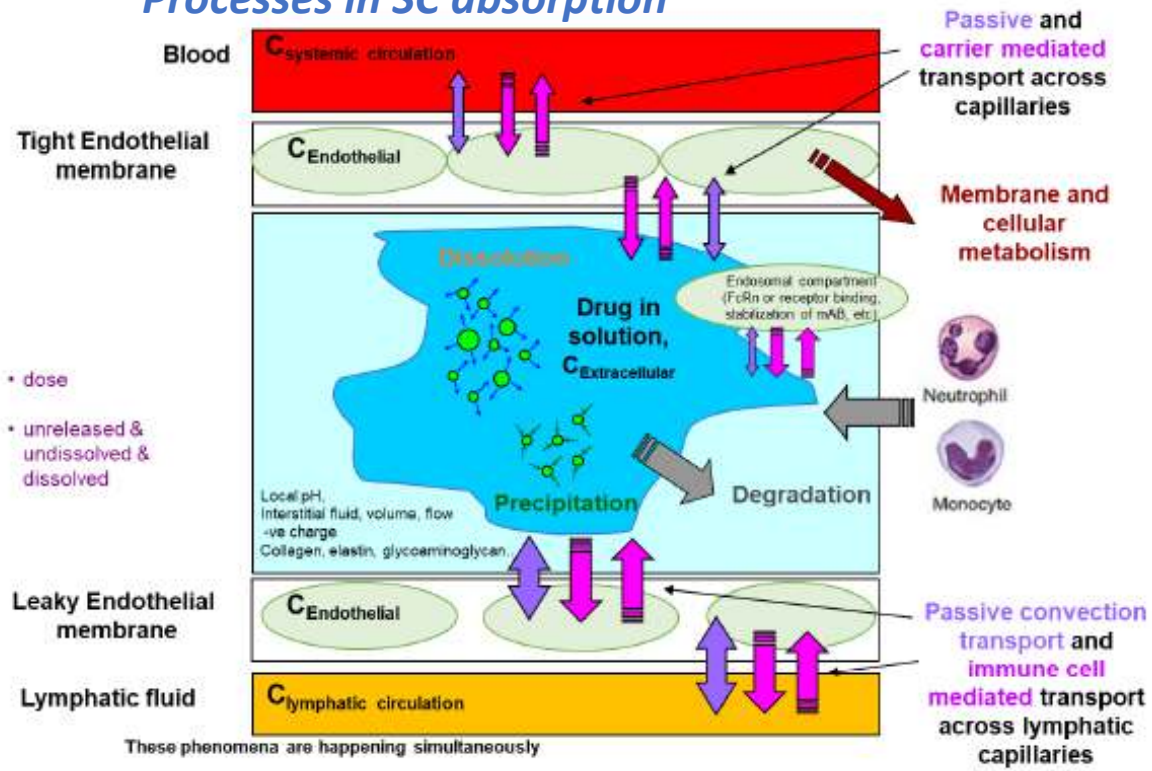


Adapted from Kagan, 2014. Drug Metab Dispos 42:1890–1905

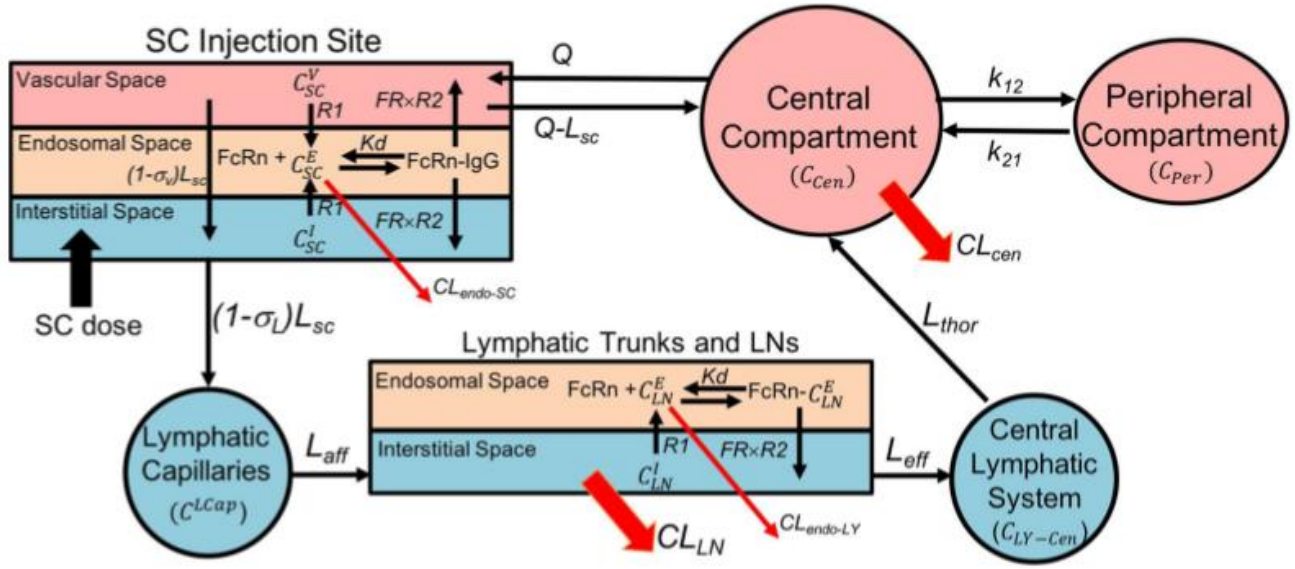
Mechanistic Models

- Mechanistic models:
  - are physiologically representative
  - can be used for bottom-up prediction
  - can be used for parameter sensitivity analysis
  - are being developed commercially e.g. by Simcyp and Simulations Plus

Processes in SC absorption



Model Schematic



Varkhede & Forrest. J Pharm Pharm Sci . 2018 ; 21(1 Suppl): 130s–148s. doi:10.18433/jpps30028

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Parameter Sensitivity Analysis

Model parameter	Molecule	Output parameter evaluated	Sensitivity analysis conclusion
MW	Various	% absorbed via lymphatic mechanism	S shaped curve observed showing that as MW increased >5 kDa, the % absorbed via lymphatic mechanism increased. Correlated with *in vivo* animal data
Hydrodynamic radius	Various	Ci relative to Cp	Prediction correlated with animal data showing Ci/Cp decreased with increase in hydrodynamic radius according to theory
Lymphatic flow rate, elimination rate during lymphatic transport	Omalizumab	T_{max}	T_{max} is predicted to be highly sensitive to lymphatic flow rate and not sensitive to the other physiological parameters evaluated, including elimination rate during lymphatic transport
Various physiological parameters (eg, lymphatic flow, transit time of drug from lymph system, endosomal uptake)	Omalizumab	SC bioavailability	K_{lymph} = T > lymphatic flow rate >> endosomal uptake rate of antibody = FcRN concentration = endosomal return rate of mAb. Bioavailability will increase as K_{lymph} or T decreases, or when lymphatic flow rate increases at its low range.
pI	Various	C_{max} and T_{max}	No correlation with pI. This could be due to limited range of pI for therapeutic proteins investigated (5.2–8.8, except for one with pI 11.2)
Lymphatic recirculation	Trastuzumab	Bioavailability	Simulations using the model indicated that on average each trastuzumab molecule recirculated 4–5 times through the lymphatic systems before being eliminated and explained the overestimation of SC bioavailability relative to IV
FcRn expression and binding affinity	Rituximab	Bioavailability	10-fold difference in binding affinity or the receptor expression level had a predicted significant effect on bioavailability e.g. reduction in bioavailability from 69% to ~20% when binding affinity is reduced 10-fold (i.e., K_D is increased from 1 to 10)

Gaps and Opportunities

Further studies on the could benefit model parameterisation and predictive capability:

- Improved collection of metadata from in vivo studies
- Injection site and lymph physiology
- Nucleation/precipitation/dissolution
- Geometry/temporal spread
- Diffusivity/convective flow through ECM
- FcRn binding and endosomal uptake
- Presystemic catabolism
- Interspecies scaling
- Formulation/device effects

Successful predictive models of the future will likely combine multiple in vitro characterizations (with minimal in vivo experimentation) to predict rate and extent of SC absorption. As understanding evolves, we can focus on the aspects most likely to be rate-limiting for a therapeutic protein or drug class.

Thank you

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