1 PK Model Equations and Parameter Estimates, Validity of the pump-to-patient model

1.1 CPT-11

The equations for irinotecan PK model are:

\[
\frac{dL_{cpt}}{dt} = d(t) - C_{cpt,t} \cdot L_{cpt} - E_{f1} \cdot L_{cpt} + U_{p1} \cdot B_{cpt} - (V_{max, cp} \cdot L_{cpt})/(Kcp + L_{cpt})))/V_t
\] (1)

\[
\frac{dL_{sn}}{dt} = (-C_{sni} \cdot L_{sn} - E_{f1} \cdot L_{sn} + U_{p1} \cdot B_{sn} + (V_{max, cp} \cdot L_{cpt})/(Kcp + L_{cpt})))/V_t
\] (2)

\[
\frac{dB_{cpt}}{dt} = (E_{f1} \cdot L_{cpt} - U_{p1} \cdot B_{cpt} + E_{f0} \cdot O_{cpt} - U_{p0} \cdot B_{cpt} - C_{cpt,b} \cdot B_{cpt}) - (V_{max, cp} \cdot B_{cpt})/(Kcp + B_{cpt})))/V_b
\] (3)

\[
\frac{dB_{sn}}{dt} = (E_{f1} \cdot L_{sn} - U_{p1} \cdot B_{sn} + E_{f0} \cdot O_{sn} - U_{p0} \cdot B_{sn} - C_{snn,b} \cdot B_{sn}) + (V_{cp} \cdot B_{cpt})/(Kcp + B_{cpt})))/V_b
\] (4)

\[
\frac{dO_{cpt}}{dt} = (U_{p0} \cdot B_{cpt} - E_{f0} \cdot O_{cpt} - C_{cpt,o} \cdot O_{cpt}) - (V_{max, cp} \cdot O_{cpt})/(Kcp + O_{cpt})))/V_o
\] (5)

\[
\frac{dO_{sn}}{dt} = (U_{p0} \cdot B_{sn} - E_{f0} \cdot O_{sn} - C_{sno} \cdot O_{sn}) + (V_{max, cp} \cdot O_{cpt})/(Kcp + O_{cpt})))/V_o
\] (6)

where \( L_t, B_t \) and \( O_t \) represent the concentration in the Liver, Blood and Organs respectively, with \( cpt \) representing CPT-11, and \( sn \) standing for SN38.
Parameters estimates for individual patients are presented in Table A and parameter mean and CV are in Table B. Model fit was assessed through Sum of Squared Residuals (SSR) (Table C) and $R^2$ values (Table D). To test the validity of the PDE-based pump-to-patient model, we compared the goodness of this fit with that of the PK model with drug infusion rate equal to the infusion profile programmed in to the pump. Using the PDE to account for the properties of the system largely increased the model validity (Table C, D and Figure I)

**Table A:** Individual Parameter Estimates of irinotecan PK model

| Parameter | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11   |
|-----------|------|------|------|------|------|------|------|------|------|------|------|
| $C_{\text{cpt}_t}, C_{\text{cpt}_o} (\text{ml/h})$ | 3035 | 2055 | 6169 | 6169 | 2491 | 2956 | 3562 | 1740 | 4842 | 2077 | 2375 |
| $C_{\text{cpt}_b} (\text{ml/h})$ | 4630 | 1635 | 4141 | 5506 | 1236 | 9338 | 4556 | 3398 | 3821 | 2650 | 14947 |
| $C_{\text{sn}_1}, C_{\text{sn}_o} (\text{ml/h})$ | 52385 | 21086 | 43837 | 56190 | 12346 | 12346 | 57787 | 45700 | 12240 | 45746 | 16288 | 42194 |
| $V_{\text{max}} (\text{ml/h})$ | 53350 | 33861 | 1.002e06 | 1.21e06 | 34610 | 57870 | 62034 | 26535 | 77230 | 35604 | 52416 |
| $E_{f_1}, U_{p_1} (\text{ml/h})$ | 1515 | 705 | 1895 | 3506 | 1125 | 1506 | 270 | 1460 | 1022 | 1718 |
| $E_{f_o}, U_{p_o} (\text{ml/h})$ | 65230 | 61910 | 1.082e05 | 6.238e07 | 61710 | 1.142e08 | 1.122e05 | 25600 | 1.768e07 | 65590 | 1.655e08 |

**Table B:** Irinotecan PK model Parameter Mean and CV across patient population

| Parameter | Mean | CV |
|-----------|------|----|
| $C_{\text{cpt}_t}, C_{\text{cpt}_o} (\text{ml/h})$ | 3400 | 46.12 |
| $C_{\text{cpt}_b} (\text{ml/h})$ | 5077 | 75.35 |
| $C_{\text{sn}_1}, C_{\text{sn}_o} (\text{ml/h})$ | 3.68906e04 | 47.03 |
| $V_{\text{max}} (\text{ml/h})$ | 5.95558e04 | 48.66 |
| $E_{f_1}, U_{p_1} (\text{ml/h})$ | 1484 | 53.97 |
| $E_{f_o}, U_{p_o} (\text{ml/h})$ | 3.2756333e07 | 170.61 |
Table C: Sum of Square Residuals (SSR) for irinotecan PK model, with either the original delivery profile, or that simulated through the PDE pump-to-patient model. The table also shows improvement in percentages for each patient and average improvement for all patients.

| Model       | Patient SSR |
|-------------|-------------|
|             | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11   |
| Original profile | 28.13 | 142.92 | 91.13 | 226.06 | 456.14 | 143.58 | 32.86 | 15.09 | 70.76 | 76.56 | 140.61 |
| PDE profile   | 34.08 | 140.97 | 95.57 | 185.59 | 381.72 | 116.13 | 29.51 | 13.2  | 56.29 | 82.65 | 107.69 |
| Improvement (%)| -21.1 | 1.3   | -4.8  | 17.9  | 16.3  | 19.1  | 10.1  | 12.5  | 20.4  | -7.9  | 23.4  |
| Average Improvement (%) | 7.9   |       |       |       |       |       |       |       |       |       |

Table D: $R^2$ values for irinotecan model, with either the original delivery profile, or that simulated through the PDE pump-to-patient model. The table also shows improvement in percentages for each patient and average improvement for all patients.

| Model      | Patient $R^2$ |
|------------|---------------|
|            | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11   |
| Original profile | 0.9  | 0.72 | 0.82 | 0.83 | 0.84 | 0.65 | 0.92 | 0.96 | 0.86 | 0.95 | 0.79 |
| PDE profile   | 0.88 | 0.72 | 0.81 | 0.86 | 0.86 | 0.72 | 0.93 | 0.97 | 0.89 | 0.95 | 0.84 |
| Improvement (%)| -2.22| 0.   | -1.22| 3.61 | 2.38 | 10.77| 1.09 | 1.04 | 3.49 | 0.   | 6.33 |
| Average Improvement (%) | 2.3   |       |       |       |       |       |       |       |       |       |
Figure A: Patient data best-fit of irinotecan PK model with original delivery profile and not PDE delivery profile. Each subplot represent an individual patient dataset, fit to the model independently. The top figure shows the fit of irinotecan plasma concentration, the bottom figure shows that of SN38, the active metabolite of irinotecan. SN38 data and model simulations include both bound and free SN38.
1.2 Oxaliplatin

The equations for oxaliplatin PK model are:

\[
\frac{dL_f}{dt} = d(t) - C_l \times L_f - E_f \times L_f + U_p \times B_f - b \times L_f + u \times L_b)/V_i 
\] (7)

\[
\frac{dL_b}{dt} = (b \times L_f - u \times L_b)/V_i
\] (8)

\[
\frac{dB_f}{dt} = (E_f \times L_f - U_p \times B_f - U_p \times B_f - C_b \times B_f - b \times B_f + u \times B_b)/V_b
\] (9)

\[
\frac{dB_b}{dt} = (b \times B_f - u \times B_b)/V_b
\] (10)

\[
\frac{dO_f}{dt} = (U_p \times B_f - E_f \times O_f - C_o \times O_f - b \times O_f + u \times O_b)/V_o
\] (11)

\[
\frac{dO_b}{dt} = (b \times O_f - u \times O_b)/V_o
\] (12)

where \(L_i, B_i\) and \(O_i\) represent the concentration in the Liver, Blood and Organs respectively, with \(i\) representing either the bound drug \(b\) or the free drug \(f\).

Parameters estimates for individual patients and mean and CV over the patient population are presented in Table E. Model fit was assessed through Sum of Squared Residuals (SSR) (Table F) and \(R^2\) values (Table G). To test the validity of the PDE-based pump-to-patient model, we compared the goodness of this fit with that of the PK model with drug infusion rate equal to the infusion profile programmed in to the pump. Using the PDE to account for the properties of the system largely increased the model validity (Table F, G and Figure II).

| Parameter      | Individual Patient Parameter Values | Mean | CV   |
|----------------|-------------------------------------|------|------|
| \(C_l, C_o\) (ml/h) | 1695, 4.03, 12.02, 3.7, 1.37, 2.08, 1.94, 0.13, 5159, 0.21, 54.42 | 68.80 | 234.41 |
| \(C_b\) (ml/h)     | 5362, 9.88, 26.47, 11.29, 5.12, 19.63, 4.34, 1.77, 2.21e-04, 1.10 | 54.42 | 302.50 |
| \(E_f_l, U_p_l\) (ml/h) | 23939, 1.15e05, 1.66e06, 15253, 9177.12, 3562, 5.23e07, 1373, 3974, 6263 | 5.4162e06 | 296.03 |
| \(E_f_o, U_p_o\) (ml/h) | 18218, 19071, 14670, 12255, 10166, 19192, 19412, 12099, 114, 14515 | 1.3971e04 | 41.15 |
| \(b\) (ml/h)       | 9794, 3934, 4138, 5193, 5584, 6090, 3486, 22895, 4895, 6273 | 7228 | 77.78 |
| \(u\) (ml/h)       | 371.66, 122.36, 233.09, 649.88, 492.95, 492.95, 115.28, 2823, 921.48, 475.67 | 670.17 | 115.37 |

Table E: Parameter Estimates of oxaliplatin PK model
**Table F:** Sum of Square Residuals (SSR) for oxaliplatin model, with original delivery profile, and oxaliplatin model with PDE simulated delivery profile. The table also shows improvement in percentages for each patient and average (mean) improvement for all patients.

| Model            | Patient SSR          |
|------------------|----------------------|
|                  | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  |
| Original profile | 73.57 | 108.22 | 304.09 | 43.45 | 62.15 | 7.81 | 843.85 | 0.93 | 82.15 | 30.53 |
| PDE profile      | 60.21 | 82.5 | 167.40 | 6.44 | 47.76 | 1.12 | 479.64 | 0.03 | 52.93 | 18.68 |
| Improvement (%)  | 18.16 | 23.77 | 44.95 | 85.18 | 23.15 | 85.66 | 43.16 | 96.77 | 35.57 | 38.81 |
| Average Improvement (%) | 49.5 |

**Table G:** $R^2$ values for oxaliplatin model, with original delivery profile, and oxaliplatin model with PDE simulated delivery profile. The table also shows improvement in percentages for each patient and average (mean) improvement for all patients.

| Model            | Patient R2        |
|------------------|-------------------|
|                  | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   |
| Original profile | 0.67 | 0.71 | 0.54 | 0.83 | 0.74 | 0.87 | 0.16 | 0.82 | 0.84 | 0.83 |
| PDE profile      | 0.66 | 0.67 | 0.83 | 0.97 | 0.73 | 0.98 | 0.53 | 0.83 | 0.87 | 0.84 |
| Improvement (%)  | -1.49 | -5.63 | 53.7 | 16.87 | -1.35 | 12.64 | 231.25 | 1.22 | 3.57 | 1.2  |
| Average Improvement (%) | 31.2 |
Figure B: Patient data best-fit of oxaliplatin PK model with original delivery profile and not PDE delivery profile. Each subplot is an individual patient data, fit to the model independently. The top figure shows plasma ultrafiltrate platinum concentrations, and the bottom figure shows plasma total platinum concentrations.
1.3 5-fluorouracil

The equations for 5-fluorouracil PK model are:

\[
\frac{dL}{dt} = \frac{(d(t) - Cl * L - EfL * L + UpL * B)/Vl}{(13)}
\]

\[
\frac{dB}{dt} = \frac{(EfL * L + EfO * O - UpO * B - UpL * B - Cb * B)/Vb}{(14)}
\]

\[
\frac{dO}{dt} = \frac{(UpO * B - EfO * O - Co * O)/Vo}{(15)}
\]

where \( L_i, B_i \) and \( O_i \) represent the concentrations of 5-fluorouracil in the Liver, Blood and Organs respectively.

Parameters estimates for individual patients and Mean and CV over the patient population are presented in Table H. Model fit was assessed through Sum of Squared Residuals (SSR) (Table I) and \( R^2 \) values (Table J). To test the validity of the pump-to-patient model, we compared the goodness of this fit with that of the PK model with drug infusion rate equal to the infusion profile programmed in to the pump. Using the PDE to account for the properties of the system largely increased the model validity (Table I, J and Figure III).

| Parameter | Patient parameter value |
|-----------|-------------------------|
| \( Cl, CO (\text{ml/h}) \) | 132834 118360 125365 349150 888311 131285 523901 117557 302323 84.18 |
| \( Cb (\text{ml/h}) \) | 84801 46116 70614 181219 86562 221789 98929 130879 36451 56.0 |
| \( EFo/L, UPo/L (\text{ml/h}) \) | 21.09 6540 38.89 86.54 2.682e+05 1048e+06 23.68 1.618e+06 58.18 326127 176.79 |

Table H: Parameter Estimates of 5-fluorouracil PK model
| Model        | Patient SSR          |
|--------------|----------------------|
|              | 1      | 2      | 3      | 4      | 5      | 7      | 8      | 9      | 10     |
| Original profile | 241.2  | 131.1  | 640.4  | 84.4   | 604.3  | 57.6   | 306.8  | 308.2  | 1556.8 |
| PDE profile   | 186.5  | 48.7   | 554.3  | 80.4   | 861.2  | 57.55  | 256.6  | 294.2  | 1076.4 |
| Improvement (%) | 22.6   | 62.9   | 13.4   | 4.7    | -4.3   | 0.01   | 16.3   | 4.5    | 30.8   |
| Average Improvement (%) | 12.5   |        |        |        |        |        |        |        |        |

Table I: Sum of Square Residuals (SSR) for 5-fluorouracil model, with original delivery profile, and 5-fluorouracil model with PDE simulated delivery profile. The table also shows improvement in percentages for each patient and average (mean) improvement for all patients.

| Model        | Patient R2          |
|--------------|---------------------|
|              | 1      | 2      | 3      | 4      | 5      | 7      | 8      | 9      | 10     |
| Original profile | 0.79   | 0.96   | 0.73   | 0.85   | 0.69   | 0.75   | 0.64   | 0.65   | 0.83   |
| PDE profile   | 0.84   | 0.99   | 0.77   | 0.86   | 0.55   | 0.86   | 0.79   | 0.65   | 0.88   |
| Improvement (%) | 6.3    | 3.1    | 5.5    | 1.2    | -20    | 0      | 5.3    | 1.5    | 6.0    |
| Average Improvement (%) | 0.97   |        |        |        |        |        |        |        |        |

Table J: $R^2$ values for 5-fluorouracil model, with original delivery profile, and 5-fluorouracil model with PDE simulated delivery profile. The table also shows improvement in percentages for each patient and average (mean) improvement for all patients.
Figure C: Patient data best-fit of 5-fluorouracil PK model with original delivery profile and not PDE delivery profile. Each subplot is an individual patient data fit to the model independently.
2 Identifiability

Parameter identifiability was checked for irinotecan, oxaliplatin and 5-fluorouracil model using the method of likelihood profiles (reference [23] of main text). Briefly, the distance between the experimental data and the model is computed by an objective function, here the weighted sum of squared residuals:

\[
C(\theta) = \sum_{i=1}^{m} \left( \frac{y_i - f(t_i, \theta)}{\sigma_i} \right)^2
\]

where \(y_i\) are the data points at the corresponding time points \(t_i\), \(f(t_i, \theta)\) are the model values at \(t_i\) with parameters \(\theta\), and \(\sigma_i\) the data standard deviations. Minimizing this objective function over parameter values is equivalent to maximizing the likelihood estimator for normally distributed datasets.

For each parameter \(\theta_j\), the likelihood profile \(C_{PL}(\theta_j)\) is defined as:

\[
C_{PL}(\theta_j) = \min_{\theta_k \neq \theta_j} [C(\theta)]
\]

The pointwise confidence interval of parameter \(\theta_j\) is defined as:

\[
\{\theta_j | C_{PL}(\theta_j) - C_{PL}(\theta_j^*) < \Delta_\alpha\}
\]

where \(\theta_j^*\) is the parameter optimal value which minimizes \(C(\theta)\). \(\Delta_\alpha\) is the \(\chi^2\) distribution value for 0.95 confidence \(\alpha\) and one degree of freedom \(df = 1\):

\[
\Delta_\alpha = \chi^2(\alpha, df) = 3.84.
\]

A parameter is identifiable if its pointwise confidence interval is finite ([23] in main text). In other words, if the likelihood profile crosses the threshold value \(C_{PL}(\theta_j^*) + \Delta_\alpha\) twice (i.e. when increasing and decreasing parameter value starting from optimal value), this proves parameter identifiability. The points at which the likelihood profile crosses the threshold are the ranges of the parameter confidence interval.

The study was done using Patient 1 parameter estimates as starting points. All model parameters were identifiable for all three drugs (Figure IV, V, VI).
Figure D: Parameter Identifiability for irinotecan PK model.
Figure E: Parameter Identifiability for oxaliplatin PK model.
Figure F: Parameter Identifiability for 5-fluorouracil PK model.

3 Clustering

Clustering was done using fuzzy c-means clustering as described in the Methods section of main text. The validity function $V_{FS}$ as proposed by Fukuyama and Sugeno was used to determine the number of clusters for each drug. The optimal cluster number is defined as the one minimizing $V_{FS}$. Results are shown in Figures VII, VIII, IX.
Figure G: Patient parameter clustering analysis for Irinotecan. (a) 2D visualisation of patient clusters for different number of clusters. Centroids (stars) and patients (dots) are shown, (b) $V_{FS}$ values for different numbers of clusters.
Figure H: Patient parameter clustering analysis for oxaliplatin. (a) 2D visualization of patient clusters for different number of clusters. Centroids (stars) and patients (dots) are shown, (b) $V_{FS}$ values for different numbers of clusters.
Figure I: Patient parameter clustering analysis for 5-fluorouracil. (a) 2D visualisation of patient clusters for different number of clusters. Centroids (stars) and patients (dots) are shown, (b) $V_{FS}$ values for different numbers of clusters.