# Analysis and modeling of cancer drug responses using cell cycle phase-specific rate effects

## Supplementary Information

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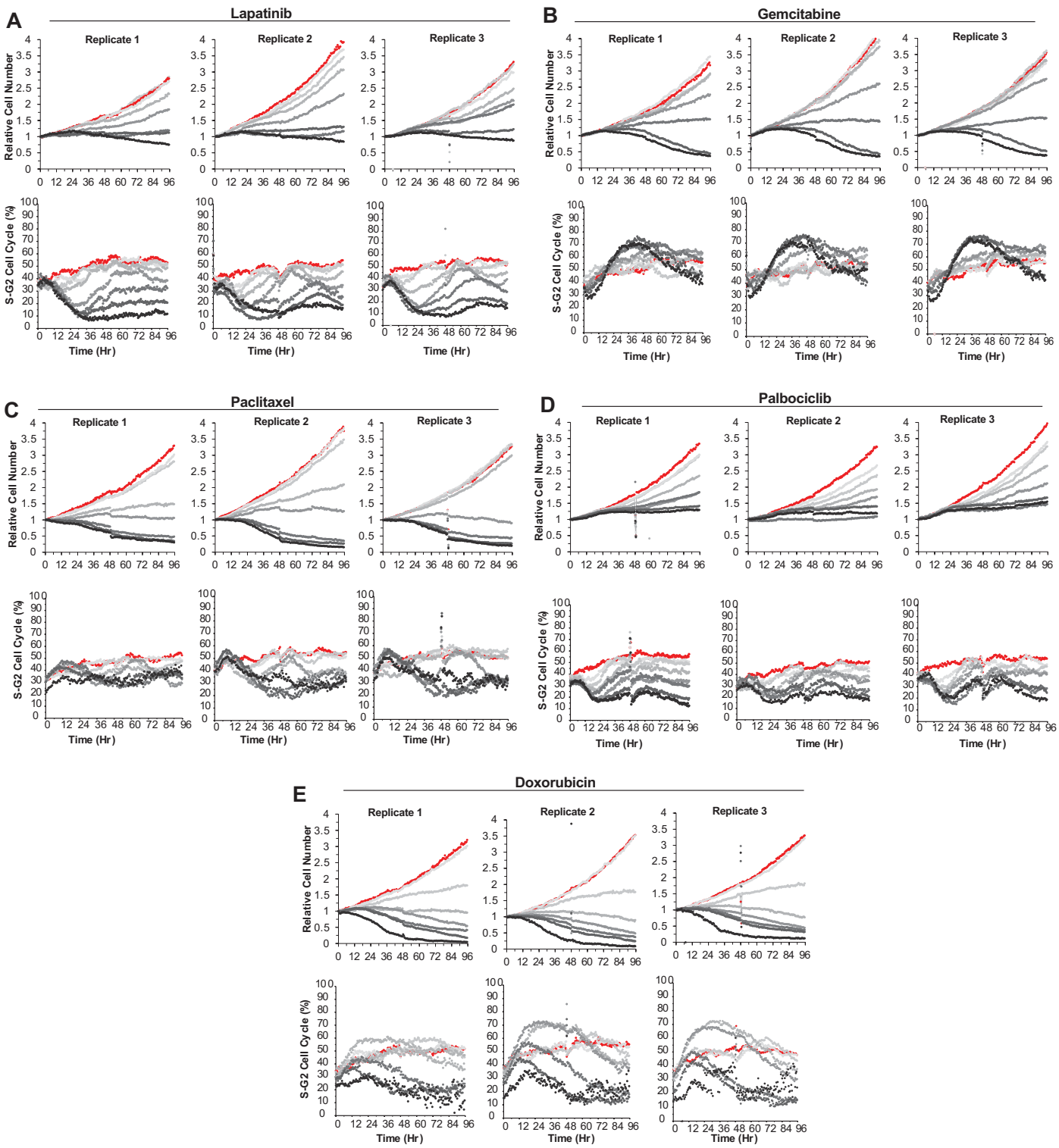
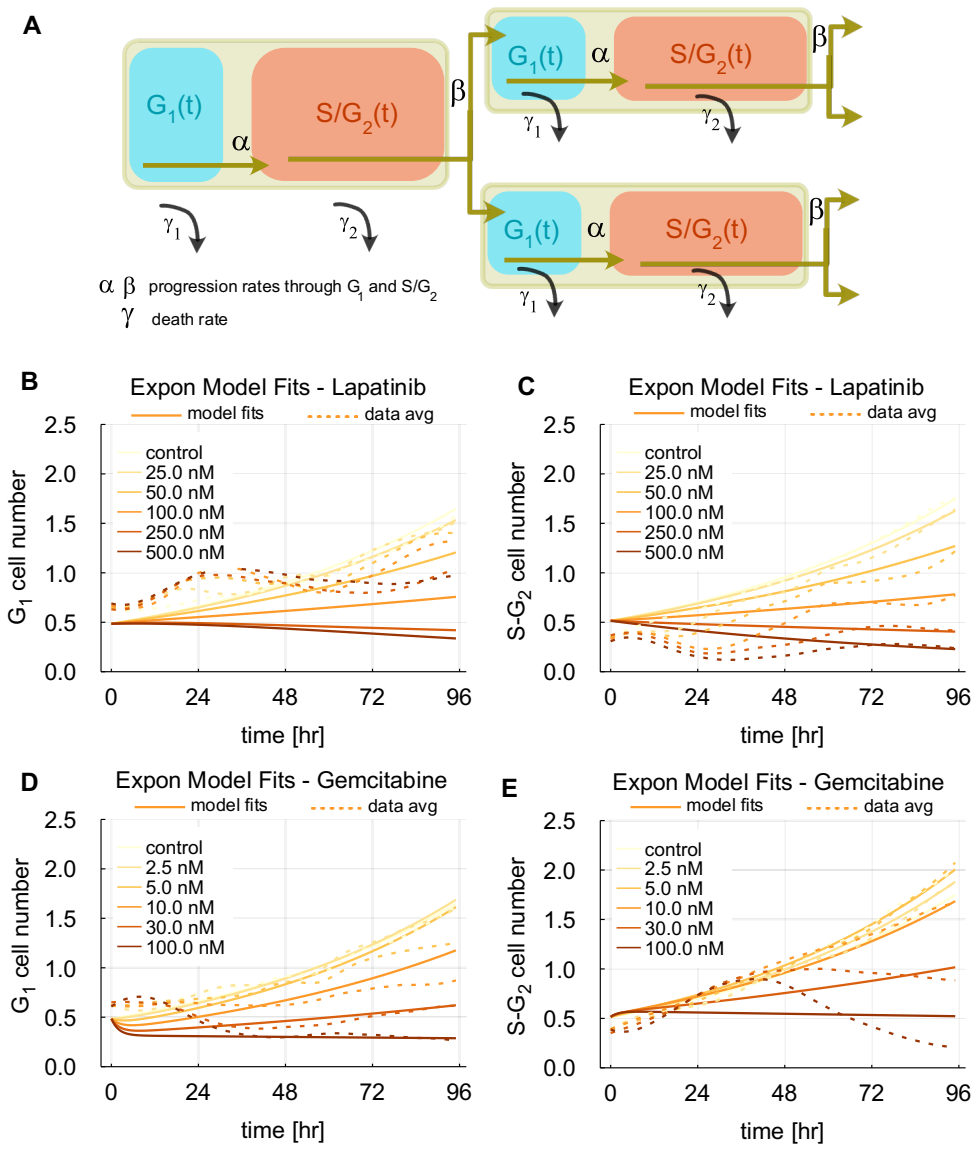
## Supp. Figure 1



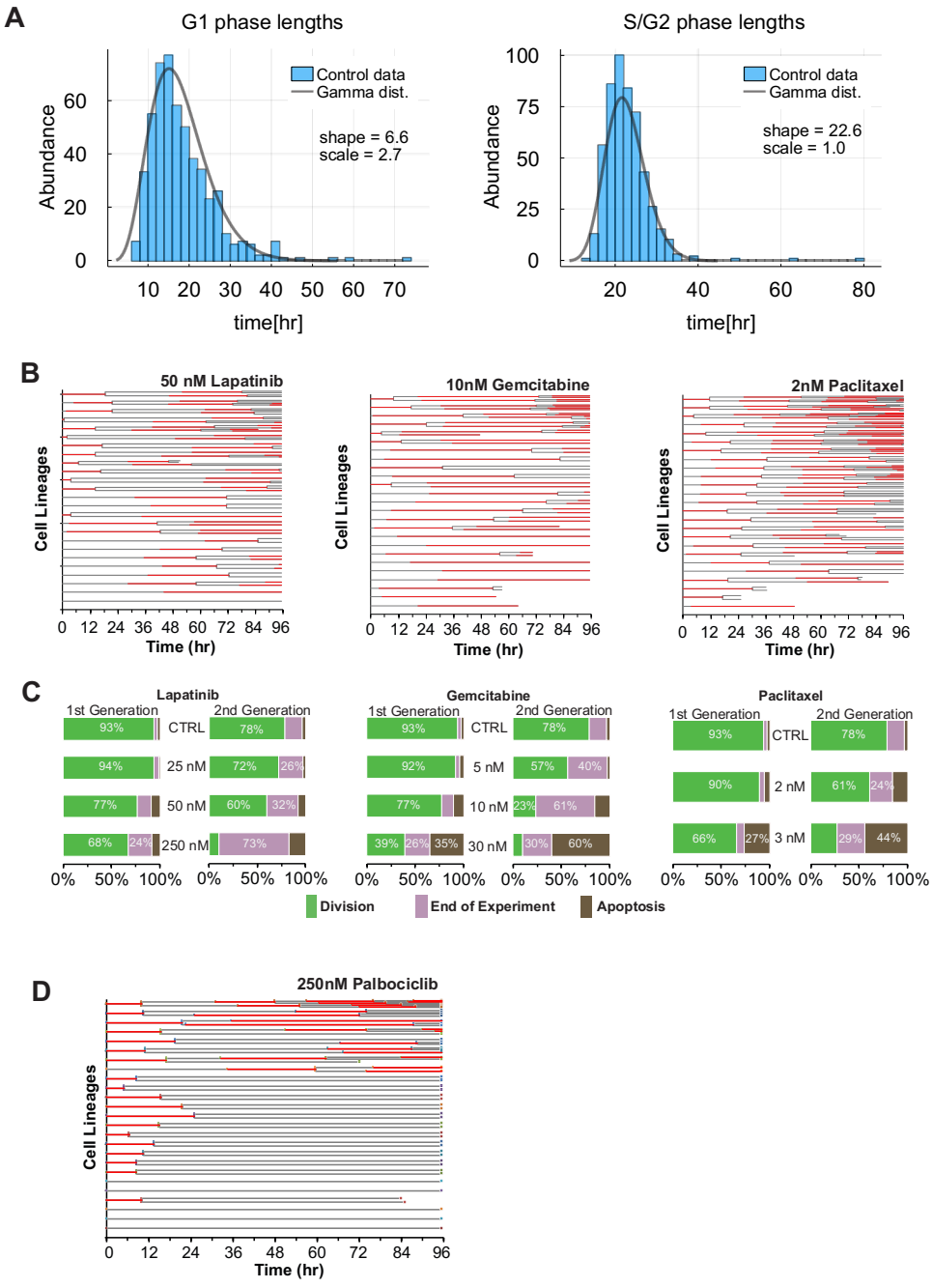

**Supplementary Figure 1. Individual replicates for AU565 drug responses show similar temporal dynamics and drug-induced changes to cell cycle.** Panels show relative cell numbers and S-$G_2$ normalized cell numbers for lapatinib (**A**), gemcitabine (**B**), paclitaxel (**C**), palbociclib (**D**), and doxorubicin (**E**) treatments for three biological replicates. Five drug concentrations (gray lines) and untreated control (red line) are plotted. Source data are provided on Synapse..

## Supp. Figure 2



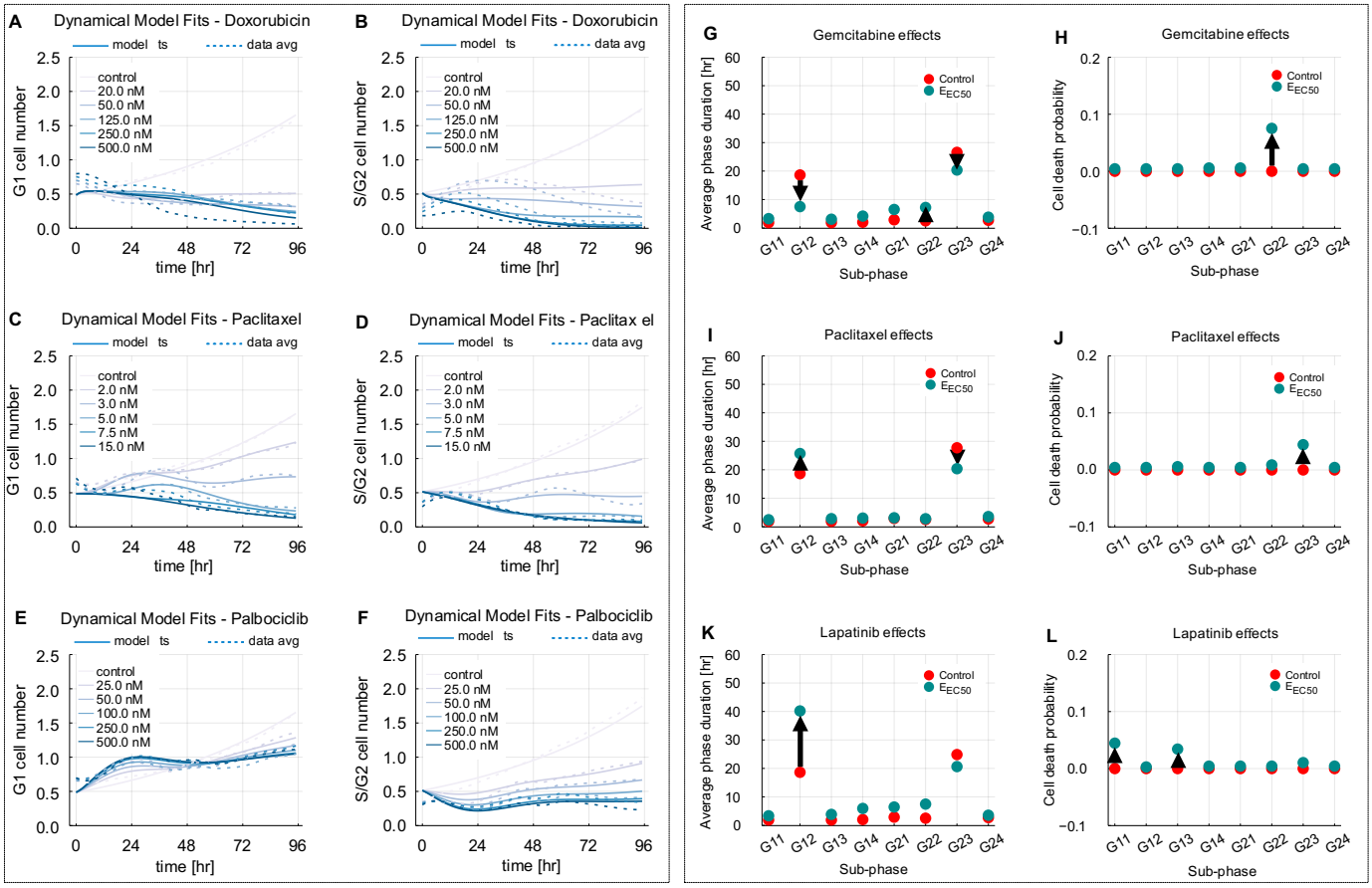

**Supplementary Figure 2. An exponential cell cycle model without incorporating delay times fails to capture the dynamics of drug response. A.** The transition diagram for a simple dynamical model with 2 phases ($G_1$ and S-$G_2$) and without the LCT. $\alpha$ and $\beta$, are the transition rates from $G_1$ to S-$G_2$ and vice versa, $\gamma_1$ and $\gamma_2$ are the death rates in $G_1$ and S-$G_2$, respectively. **B-E.** Exponential cell cycle model simulations of $G_1$ and S-$G_2$ cell numbers over time for control and 5 concentrations of lapatinib (**B-C**) and gemcitabine (**D-E**) (solid lines), respectively, overlayed with the average of three experimental replicates (dashed lines). Source data are provided on Synapse.

## Supp Figure 3



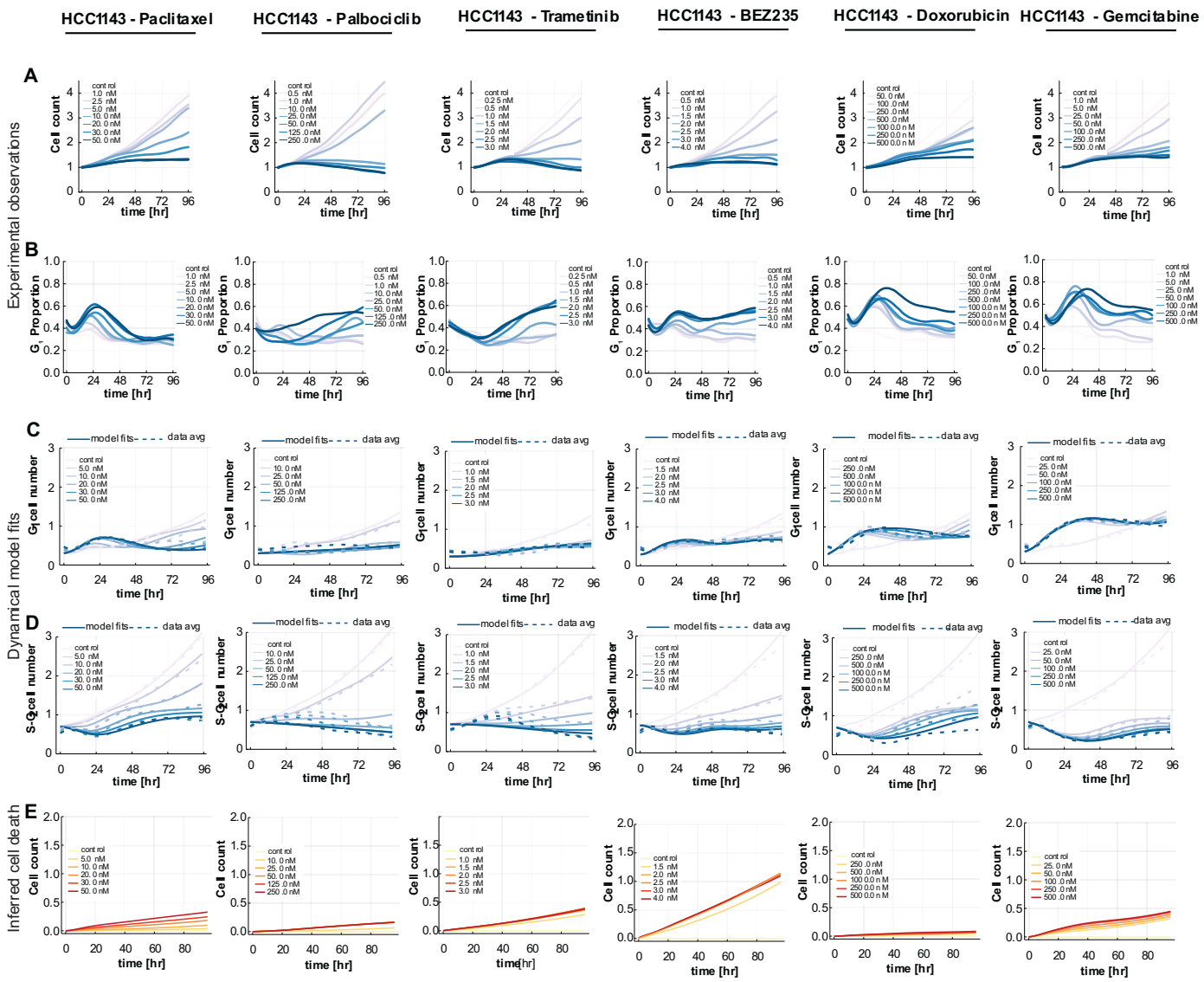

**Supplementary Figure 3. Analysis of single cell tracking data reveals drug-specific cell cycle phase effects in AU565 cells. A.** Lineage trees of 25 lineages across 96H for various drug treatments. Tracks are colored coded based on cell cycle phase: gray indicates $G_1$ and red indicates S-$G_2$ phase. Track splitting indicates mitosis, and track ending prior to 96H corresponds to apoptosis. **B.** Quantification of cell outcomes (division, cell death, viable at end of experiment) for cells from the first and second generations treated with lapatinib, gemcitabine, or paclitaxel. **C.** Gamma distribution of $G_1$ and S-$G_2$ phase durations for cells in control condition with sample size of 520 and 514 for $G_1$ and S-$G_2$ phases, respectively. **D.** Lineage trees for 25 lineages across 96H after treatment with Palbociclib. Source data are provided on Synapse.

## Supp. Figure 4



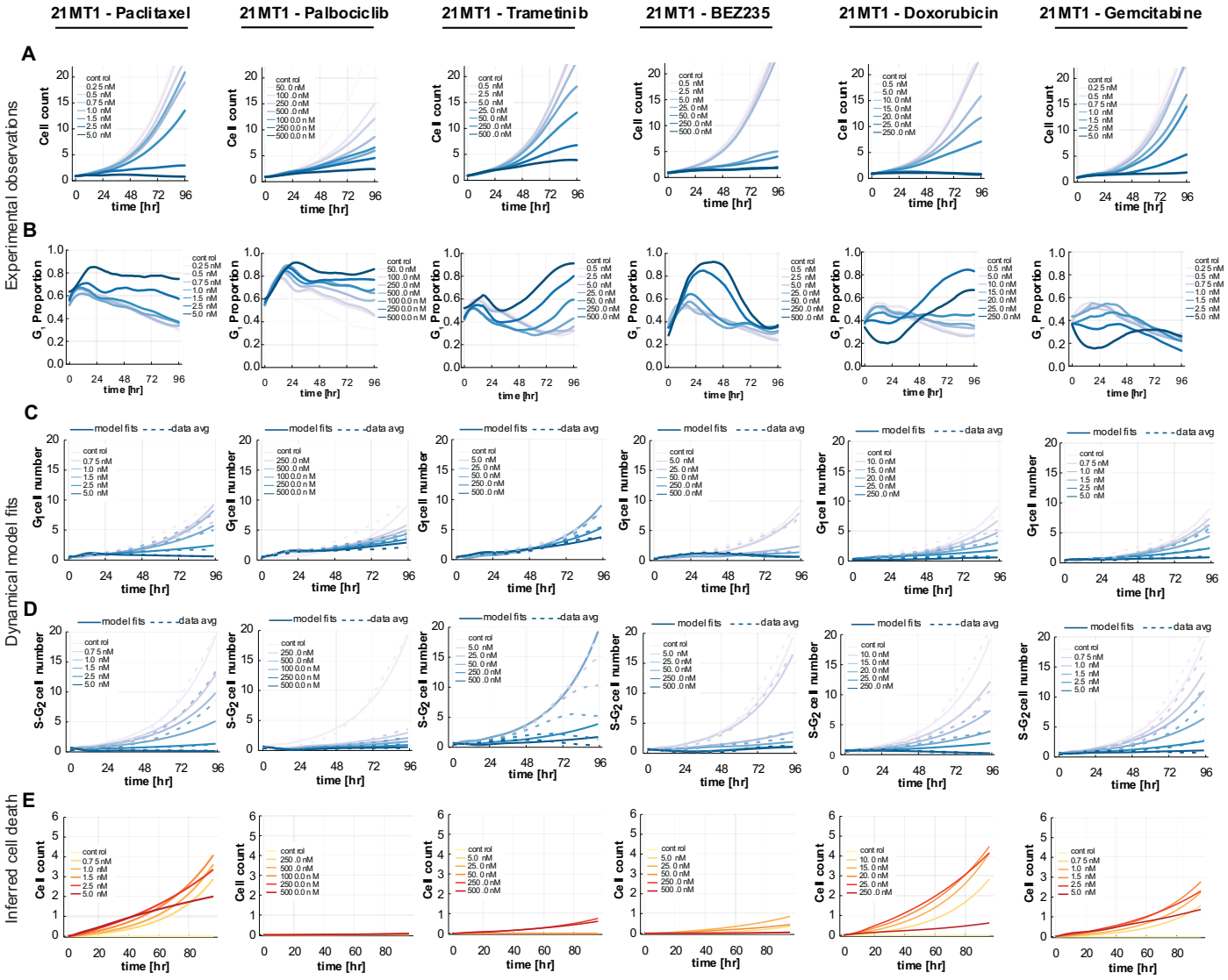

**Supplementary Figure 4. A dynamical model of the cell cycle captures the dynamics of drug response.** **A-F.** $G_1$ and S-$G_2$ cell numbers overtime, respectively, for the control and treatment at 5 concentrations (solid lines) for doxorubicin (**A-B**) paclitaxel (**C-D**), and palbociclib (**E-F**) overlayed with the average of three corresponding experimental replicates (dashed lines). **G-L**. The average phase durations in $G_1$ and S-$G_2$ phases for selected drug treatments. The arrow shows the shift from the control condition to the drug effect at the half maximum concentration ($E_{EC50}$). Source data are provided on Synapse.

## Supp. Figure 5



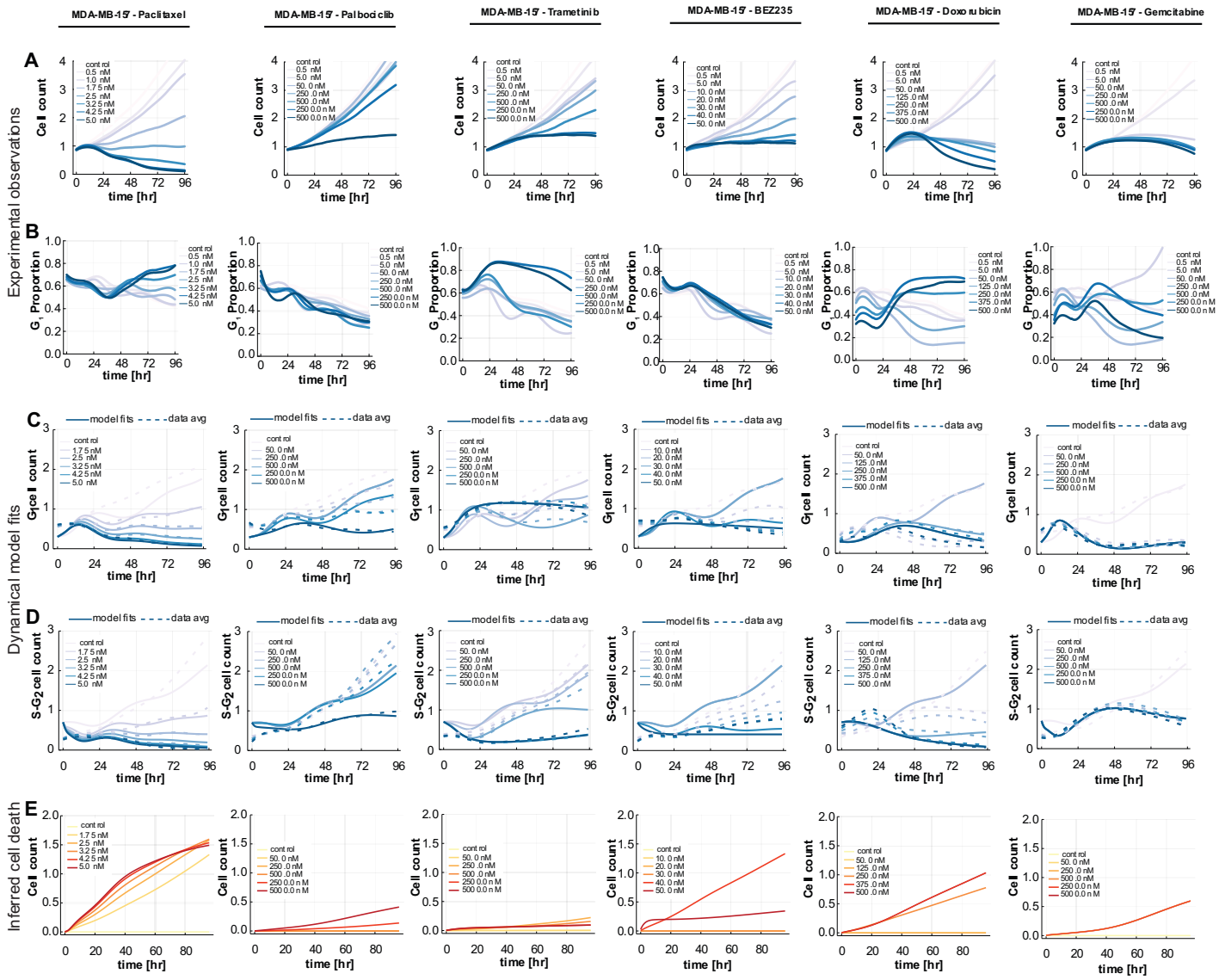

**Supplementary Figure 5. The introduced dynamical model captures the cell cycle dynamics of drug response in TNBC cell line HCC1143. A, B.** Experimentally observed drug-induced changes to cell numbers (**A**) and $G_1$ cell cycle phase proportion (**B**) after dose-escalation treatment with a panel of inhibitors. **C,D.** $G_1$ and S-$G_2$ fits overtime, respectively, for the untreated and treatment at 5 concentrations (solid lines) overlayed with the average of three corresponding experimental replicates (dashed lines) for 6 drug treatments. **E.** Inferred accumulated dead cells over time for 6 drug treatments. Source data are provided on Synapse.

## Supp. Figure 6



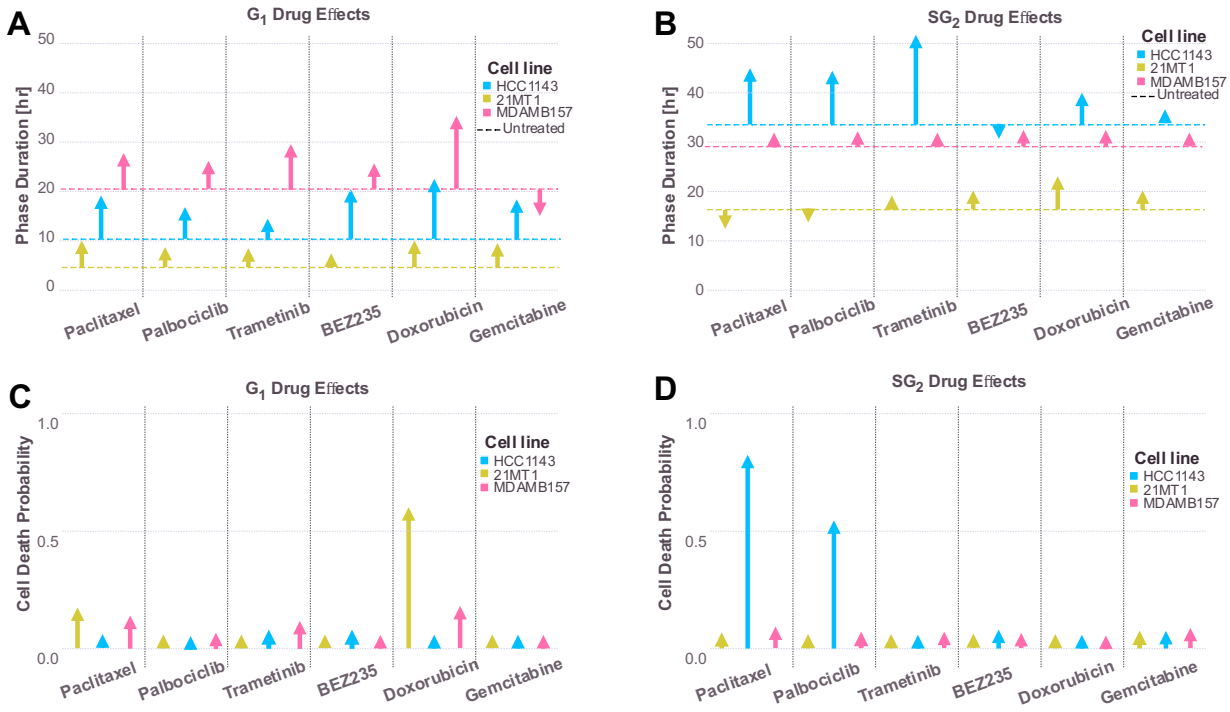

**Supplementary Figure 6. The introduced dynamical model captures the cell cycle dynamics of drug response in 21MT1 cell line. A, B.** Experimentally observed drug-induced changes to cell numbers (**A**) and $G_1$ cell cycle phase proportion (**B**) after dose-escalation treatment with a panel of inhibitors. **C,D.** $G_1$ and S-$G_2$ fits overtime, respectively, for the untreated and treatment at 5 concentrations (solid lines) overlayed with the average of three corresponding experimental replicates (dashed lines) for 6 drug treatments. **E.** Inferred accumulated dead cells over time for 6 drug treatments. Source data are provided on Synapse.

## Supp. Figure 7




**Supplementary Figure 7. The introduced dynamical model captures the cell cycle dynamics of drug response in TNBC cell line MDAMB175. A,B.** Experimentally observed drug-induced changes to cell numbers (**A**) and $G_1$ cell cycle phase proportion (**B**) after dose-escalation treatment with a panel of inhibitors. **C,D.** $G_1$ and S-$G_2$ fits overtime, respectively, for the untreated and treatment at 5 concentrations (solid lines) overlayed with the average of three corresponding experimental replicates (dashed lines) for 6 drug treatments. **E.** Inferred accumulated dead cells over time for 6 drug treatments. Source data are provided on Synapse.

## Supp. Figure 8




**Supplementary Figure 8. Summary of inferred cell cycle drug effects at half maximum concentration compared to untreated. A-B**. The average phase durations in $G_1$ **(A)** and S-$G_2$ **(B)** phases for HCC1143 (blue), 21MT1 (olive) and MDA-MB-157 (pink) treated with paclitaxel, palbociclib, trametinib, BEZ235, doxorubicin, and gemcitabine. The dashed lines show the average phase duration at untreated for each cell line. **C-D**. The cell death probability in $G_1$ **(C)** and S-$G_2$ **(D)** phases for HCC1143 (blue), 21MT1 (olive) and MDA-MB-157 (pink) treated with the same panel of drugs. The arrows show the quantity of increase or decrease in the effects from untreated to the half maximal concentration ($E_{EC50}$). Source data are provided on Synapse.

# Supplementary Tables

| Symbol | Units | Explanation |
|---|---|---|
| $\alpha_1$ | 1/cell/hr | Cells progression rate through the first quarter of G1. |
| $\alpha_2$ | 1/cell/hr | Cells progression rate through the second quarter of G1. |
| $\alpha_3$ | 1/cell/hr | Cells progression rate through the third quarter of G1. |
| $\alpha_4$ | 1/cell/hr | Cells progression rate through the fourth quarter of G1. |
| $\beta_1$ | 1/cell/hr | Cells progression rate through the first quarter of S/G2. |
| $\beta_2$ | 1/cell/hr | Cells progression rate through the second quarter of S/G2. |
| $\beta_3$ | 1/cell/hr | Cells progression rate through the third quarter of S/G2. |
| $\beta_4$ | 1/cell/hr | Cells progression rate through the fourth quarter of S/G2. |
| $\gamma_{11}$ | 1/cell/hr | Cells rate of death within the first quarter of G1. |
| $\gamma_{12}$ | 1/cell/hr | Cells rate of death within the second quarter of G1. |
| $\gamma_{13}$ | 1/cell/hr | Cells rate of death within the third quarter of G1. |
| $\gamma_{14}$ | 1/cell/hr | Cells rate of death within the fourth quarter of G1. |
| $\gamma_{21}$ | 1/cell/hr | Cells rate of death within the first quarter of S/G2. |
| $\gamma_{22}$ | 1/cell/hr | Cells rate of death within the second quarter of S/G2. |
| $\gamma_{23}$ | 1/cell/hr | Cells rate of death within the third quarter of S/G2. |
| $\gamma_{24}$ | 1/cell/hr | Cells rate of death within the fourth quarter of S/G2. |

**Supplementary Table 1.** Explanation of the rate parameters within the ODE model.

| Cell line | Drug | EC50 concentration [nM] |
|---|---|---|
| HCC1143 | Paclitaxel | 1.46 |
| HCC1143 | Palbociclib | 86.46 |
| HCC1143 | Trametinib | 3.71 |
| HCC1143 | BEZ235 | 34.94 |
| HCC1143 | Doxorubicin | 159.16 |
| HCC1143 | Gemcitabine | 0.74 |
| 21MT1 | Paclitaxel | 1.55 |
| 21MT1 | Palbociclib | 19.1 |
| 21MT1 | Trametinib | 220.8 |
| 21MT1 | BEZ235 | 12.52 |
| 21MT1 | Doxorubicin | 51.68 |
| 21MT1 | Gemcitabine | 1.51 |
| MDAMB157 | Paclitaxel | 2.01 |
| MDAMB157 | Palbociclib | 3594.01 |
| MDAMB157 | Trametinib | 658.20 |
| MDAMB157 | BEZ235 | 10.90 |
| MDAMB157 | Doxorubicin | 247.58 |
| MDAMB157 | Gemcitabine | 0.64 |

**Supplementary Table 2.** The concentration at half maximal effect for each cell line and treatment.