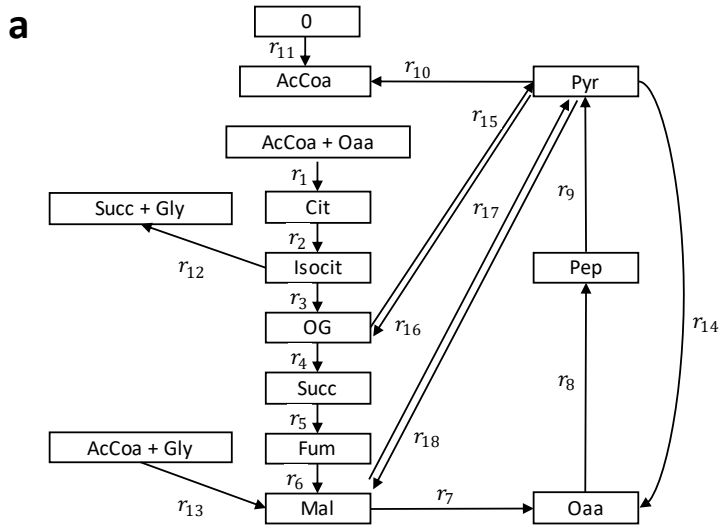


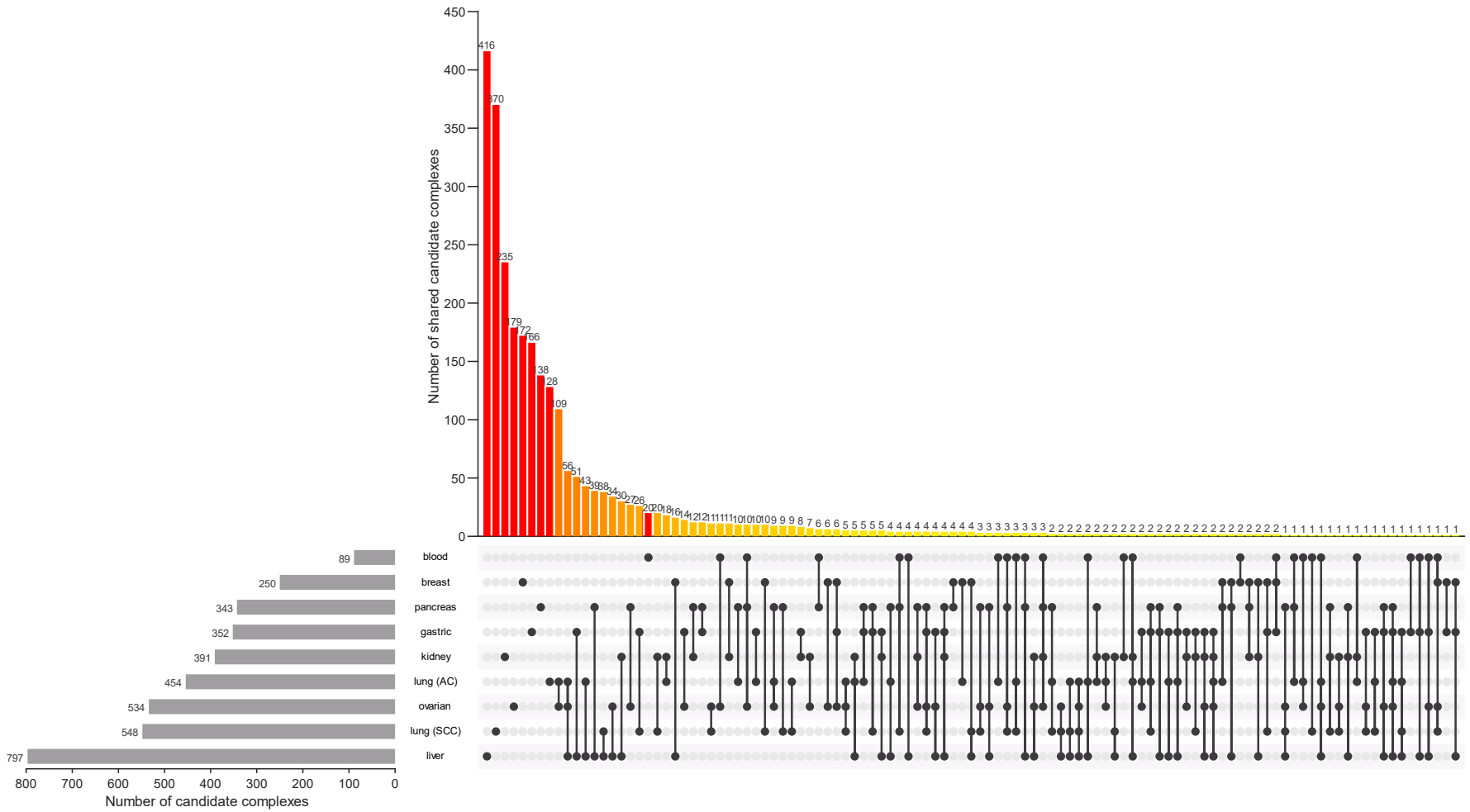
b

$$Y = \begin{array}{c} \begin{matrix} \text{AcCoA} & \text{AcCoA+Gly} & \text{AcCoA+Oaa} & \text{Cit} & \text{Fum} & \text{IsoCit} & \text{Mal} & \text{Oaa} & \text{OG} & \text{Pep} & \text{Pyr} & \text{Succ} & \text{Succ+Gly} & 0 \end{matrix} \\ \begin{bmatrix} 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 \end{bmatrix} \begin{matrix} \text{AcCoA} \\ \text{Cit} \\ \text{Fum} \\ \text{Gly} \\ \text{IsoCit} \\ \text{Mal} \\ \text{Oaa} \\ \text{OG} \\ \text{Pep} \\ \text{Pyr} \\ \text{Succ} \end{matrix} \end{array}$$

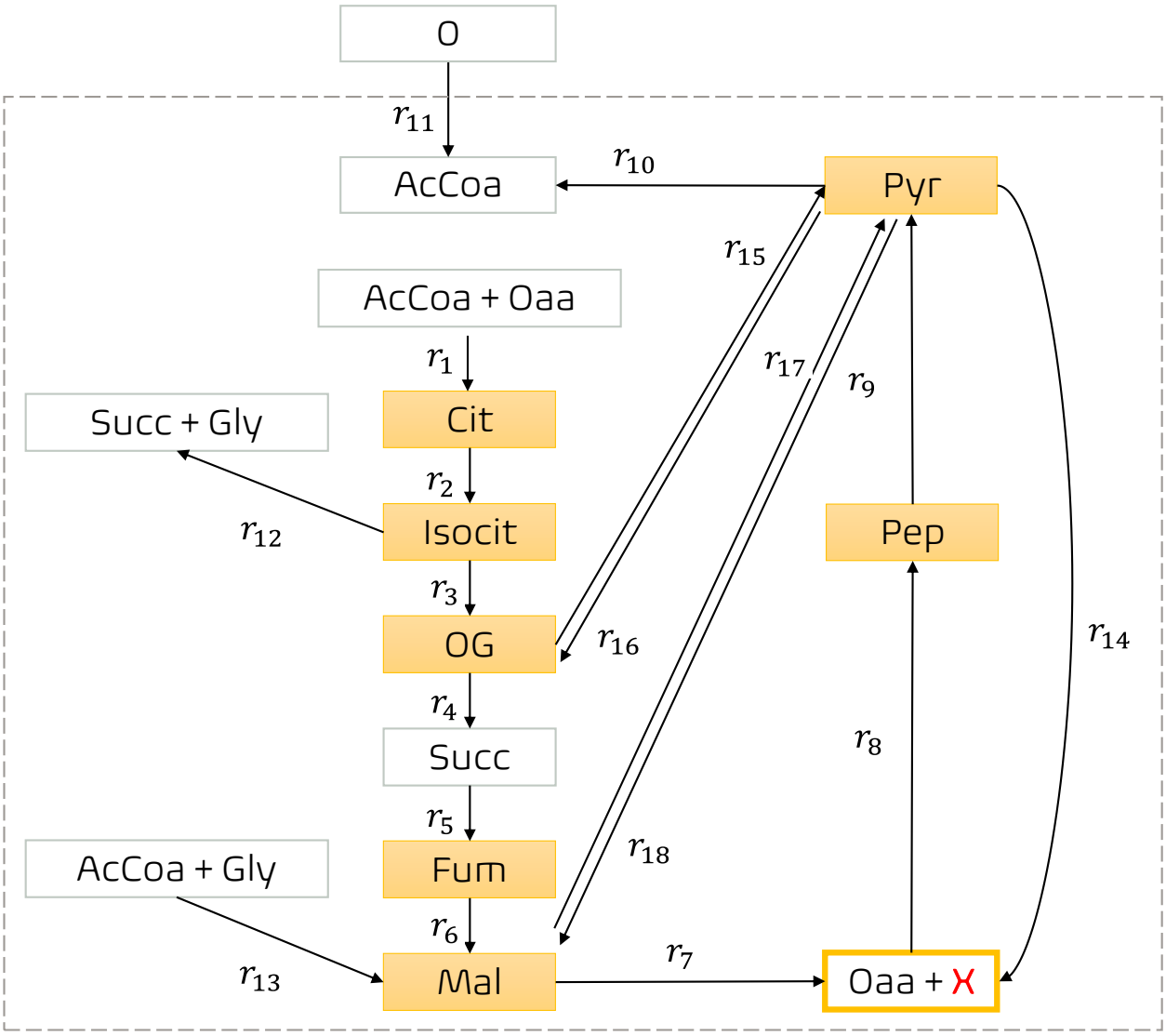
c

$$A = \begin{array}{c} \begin{matrix} r_1 & r_2 & r_3 & r_4 & r_5 & r_6 & r_7 & r_8 & r_9 & r_{10} & r_{11} & r_{12} & r_{13} & r_{14} & r_{15} & r_{16} & r_{17} & r_{18} \end{matrix} \\ \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\ -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & -1 & 1 & -1 & 1 & -1 \\ 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \begin{matrix} \text{AcCoA} \\ \text{AcCoA + Gly} \\ \text{AcCoA + Oaa} \\ \text{Cit} \\ \text{Fum} \\ \text{IsoCit} \\ \text{Mal} \\ \text{Oaa} \\ \text{OG} \\ \text{Pep} \\ \text{Pyr} \\ \text{Succ} \\ \text{Succ + Gly} \\ 0 \end{matrix} \end{array}$$

Supplementary Figure S1. Illustration of concepts related to balancing of complexes. (**a**) Network including 11 species (AcCoA, - Acetyl-CoA, Cit – Citrate, Fum – Fumarate, Gly - Glyocalate, Isocit – Isocitrate, Mal – Malate, Oaa – Oxaloacetate, OG – Oxoglutarate, Pep – Phosphoenolpyruvate, Pyr – Pyruvate, Succ – Succinate, 0 – zero-complex), 14 complexes including the zero-complex that models the interaction with the environment, depicted as rectangles, and 18 irreversible reactions, $r_1 - r_{18}$, each connecting two complexes. (**b**) Species-complex matrix **Y** of the network in (**a**), where rows correspond to species and column correspond to complexes. Each entry indicates the molarity with which a species participates in a complex. (**c**) Incidence matrix **A** of the directed graph given in (**a**). The stoichiometric matrix of the network is then given by the product of the species-complex matrix and the incidence matrix, $\mathbf{N} = \mathbf{Y} \cdot \mathbf{A}$.



Supplementary Figure S2. Specificity of cancer interventions based on complex balancing. Illustrated is the number of candidate complexes, obtained by forced balancing, per tissue as well as the cardinality of the intersection of candidate complexes between different cancer types. Tissues and associated cancer (sub)types: blood – acute myeloid leukemia, breast – invasive carcinoma, pancreas – carcinoma, gastric – adenocarcinoma, kidney – renal clear cell carcinoma, lung – adenocarcinoma (AC), lung – squamous cell carcinoma (SCC), ovarian – carcinoma, liver – hepatocellular carcinoma. The bars for the number of candidate complexes in individual models of cancer tissues are shown in red.



Supplementary Figure S3. Illustration of balancing complexes by inclusion of phantom-species. The complex $1 \cdot \mathrm{Oaa}$ being unbalanced in the original example network (see Supplementary Figure S1) becomes balanced by introducing phantom species X. The resulting complex $1 \cdot \mathrm{Oaa} + 1 \cdot \mathrm{X}$ is trivially balanced as species X does not appear in any other complex in the network. Balanced complexes are shown in yellow. The balancing complex is marked by a yellow box. Metabolite abbreviations: AcCoA, - Acetyl-CoA, Cit – Citrate, Fum – Fumarate, Gly - Glyocalate, Isocit – Isocitrate, Mal – Malate, Oaa – Oxaloacetate, OG – Oxoglutarate, Pep – Phosphoenolpyruvate, Pyr – Pyruvate, Succ – Succinate, 0 – zero-complex.