Electronic Supplementary Information for:

Resolution of Asparagine in a coupled batch grinding process: Experiments and modelling

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S1 Experimental details

The grinding was performed in round bottom flasks (50 mL), put in two tempering beakers, connected in parallel to a JULABO (F25) thermostat. Two magnetic stirrers (IKA RCT basic) with digital display to adjust to an identical stirring speed for both flasks were used to drive the magnetic stirrer inside the flasks. The solution was pumped using two peristaltic pumps, either a self-constructed pump or a commercially available one (Heidolph, Pumpdrive 5001).

For the crystal-free solution exchange poroplast cannula filters were used. They were connected to the plastic tubing of the pump via 3 mm stainless steel tubes. To monitor the liquid level easily, a graduation of the volume was added to the round bottom flask.

A typical experiment was conducted with 1.5 g (RS)-Asparagine ((RS)-Asn) and 0.075 g (R) or (S)-Asn in each vessel respectively. The amino acid was suspended in 25 mL MilliQ water together with 11.4 g glass beads (2 mm VWR) and stirred with 700 rpm at 20 °C. The crystals were ground for at least 3 days, without any liquid exchange, to get a homogeneous crystal size distribution at the start of the purification step.

The pumping needed some attention. The poroplast cannula filters were prepared by shortening them from about 2 cm to about 1.3 cm, so less “false air”, i.e. air bubbles in the solution introduced during pumping, would be produced. To get the pumping started the filters were submerged completely so they were soaked with the liquid. After the pumping was started the filters were rearranged in such a way that just 0.3 – 0.5 cm was submerged. The disadvantage of this setting is the fact that some air is constantly pumped. The liquid level, however, can be held rather constant by this trick as it outbalances the false air pumping. For the same reason it is difficult to determine exactly how much of the solution was pumped per minute. The pump was running at maximum speed and the flow rate

depended on the amount of air that entered the tubes and the condition of the filters. The filters were cleaned daily (1 to 2 times), to remove the crystals sticking to it.

Figure S1-1: *Experimental setup for the resolution of a racemic conglomerate of asparagine crystals by grinding.*

Samples were taken over time by extracting 0.5 mL of the slurry with a pasteur pipette and filtered quickly over a glass filter (P4). The residue was washed with some acetone to remove the solvent and to dry the crystals faster. The crystals were later analyzed using chiral HPLC.

HPLC sample preparation: 1 mg solid in 1 mL Milli Q water, injection volume 5 µL, HPLC column Chirobiotic T (250x4.6 mm ID), 5 µm, Astec; eluent ethanol/water 50/50 v/v, flow 0.8 mL/min, detection λ=205 nm, column temperature 35 °C. Retention times (*S*)-**Asn** 6.1 min, (*R*)-**Asn** 7.2 min.

S2 Asymmetry in grinding rate: Graphs

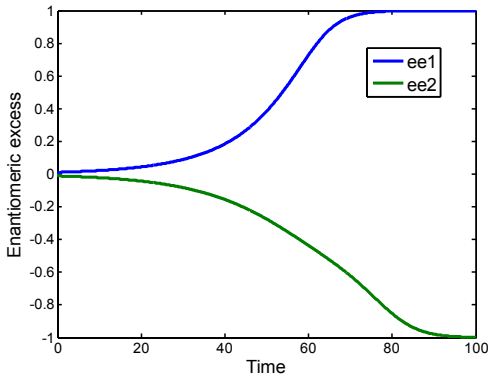

Figure S2-1: *Simulated evolution of the solid phase enantiomeric excess in the asymmetric coupled batch grinding process, using different grinding rates in both vessels: b_1 = 0.5 and b_2 = 0.495. T = 30, ee_1 = 0.01 and ee_2 = -0.01, a=3, c=0.2, M_{eq}^{B} = 1.0* and *M_{eq}^{C} = 1.1.*

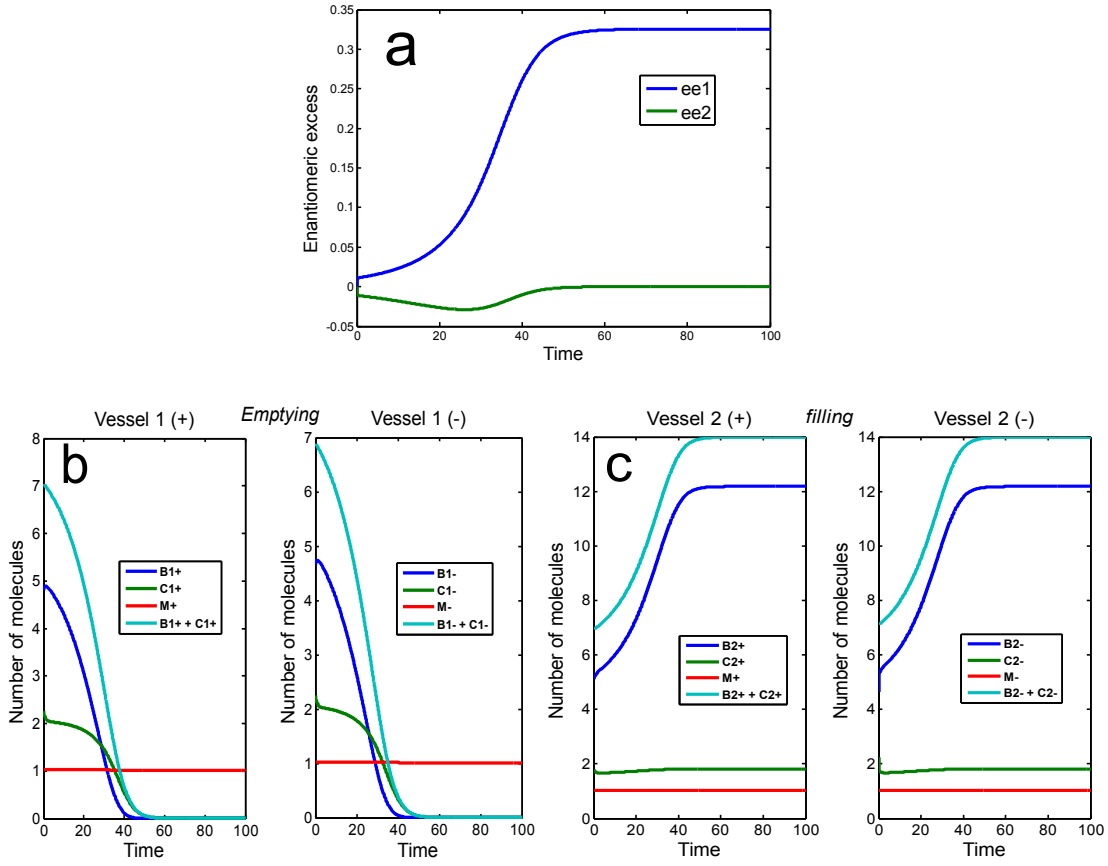

Figure S2-2: *Simulated evolution of the components involved in the asymmetric coupled batch grinding process, using different grinding rates in the vessels: b_1 = 0.50 and b_2 = 0.40. (a) Evolution of $ee_i(t)$ in both vessels; Evolution of B^+, C^+, M^+, B^-, C^- and M^- in (b) vessel 1 and (c) vessel 2. The enantiomeric excess of the "filled" vessel 2 goes to one. The remnants in the "empty" vessel show an ee($t\rightarrow\infty$) of 0.33; however, in view of its extremely low solid content of $< 10^{-4}$, this has no significance for practical use. T = 30, ee_1 = 0.01 and ee_2 = -0.01, a=3, c=0.2, M_{eq}^{B} = 1.0* and *M_{eq}^{C} = 1.1. Note: M^+ and M^- comprise the amount of molecules in the liquid of both vessels together.*

S3 Asymmetry in the equilibrium number of molecules: Graphs

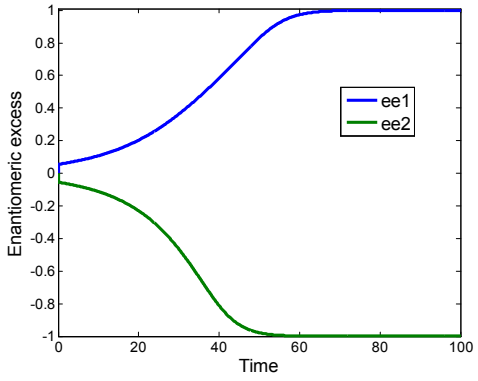

Figure S3-1: *Simulated evolution of the solid phase enantiomeric excess in the asymmetric coupled batch grinding process, using different equilibrium concentrations in both vessels: k = 1.0010. T = 30, ee_1 = 0.05 and ee_2 = -0.05, a=3, b = 0.5 and c=0.2.* M_{eq}^{B} *= 1.0 and* M_{eq}^{C} *= 1.1 for vessel 1.*

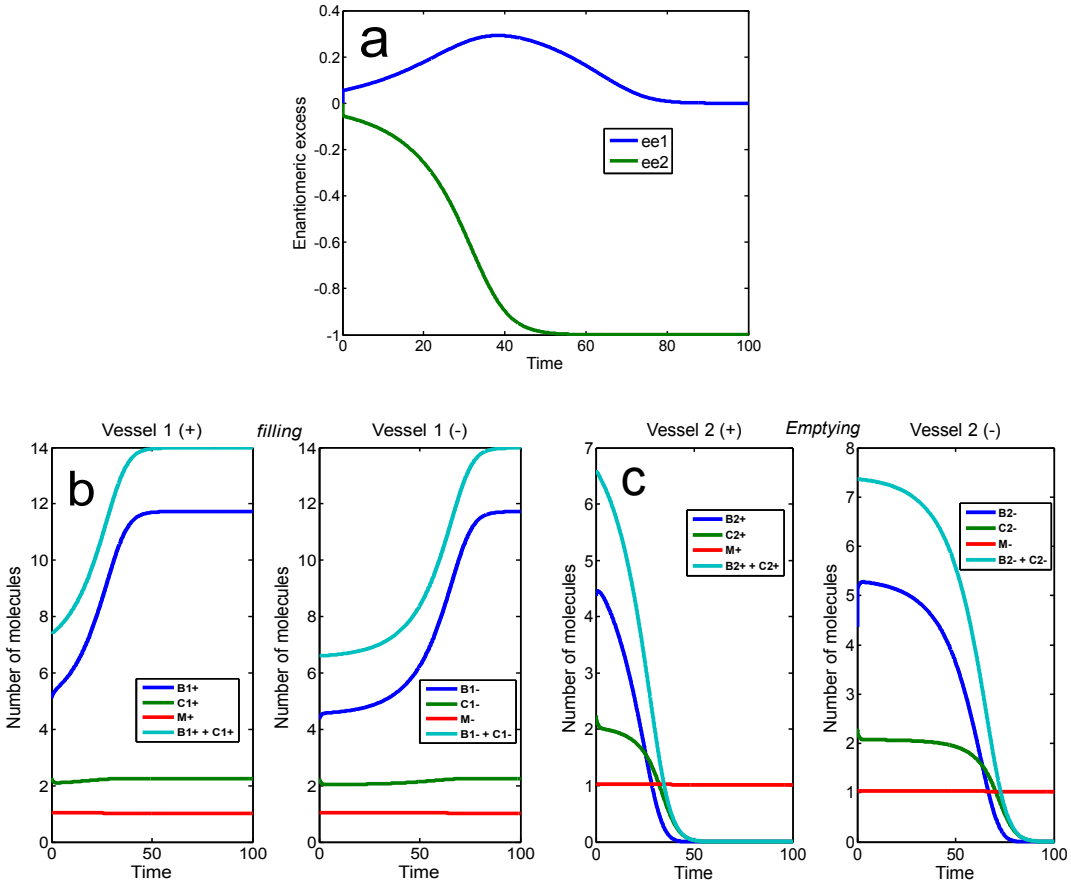

Figure S3-2: *Simulated evolution of the components involved in the asymmetric coupled batch grinding process, using different equilibrium concentrations in the vessels: k = 1.003 (a) Evolution of $ee_i(t)$ in both vessels; Evolution of B^+, C^+, M^+, B^-, C^- and M^- in (b) vessel 1 and (c) vessel 2. The enantiomeric excess of the "filled" vessel 1 goes to one. The remnants in the "empty" vessel show an ee(t→∞) of 0.33; however, in view of its extremely low solid content of $< 10^{-3}$, this has no significance for practical use. T = 30, ee_1 = 0.05 and ee_2 = -0.05, a=3, b = 0.5, c=0.2.* M_{eq}^{B} *= 1.0 and* M_{eq}^{C} *= 1.1 for vessel 1. Note: M^+ and M^- comprise the amount of molecules in the liquid of both vessels together.*