DAFTAR PUSTAKA

Abashar, M. E. E. dan Elnashaie, S. S. E. H. (2010), 'Dynamic and chaotic behavior of periodically forced fermentors for bioethanol production', *Chem. Eng. Sci.* **65**, 4894–4905.

Agmon, N. (2000), 'Conformational cycle of a single working enzyme', *J. Phys. Chem. B* **104**, 7830–7834.

Aiba, S., Shoda, M. dan Nagatani, M. (1968), 'Kinetics of product inhibition in alcoholic fermentation', *Biotechnol Bioeng* **11**, 846–864.

Astudillo, I. dan Alzate, C. (2011), 'Review: Importance of stability study of continuous systems for ethanol production', *Journal of Biotechnology* **151**, 43–55.

Bailey, J. (1991), 'Toward a science of metabolic engineering', *Science* **252**, 1668–1675.

Bellgardt, K. H. (1994), 'Analysis of synchronous growth of bakers yeast part I: development of a theoretical model for sustained oscillations', *J. Biotechnol.* **35**, 19–33.

Benkovic, S. dan Hammes-Schiffer, S. (2003), 'A perspective on enzyme catalysis', *Science* **301**, 1196–1202.

Bennett, W. dan Steitz, T. (1978), 'Glucose-induced conformational change in yeast hexokinase', *PNAS* **75**, 4848–4852.

Bezdek, J. C. (1981), *Pattern Recognition with Fuzzy Objective Function Algorithms*, Springer Publishers, New York.

Bezdek, J. C., Ehrlich, R. dan Full, W. (1984), 'FCM: The fuzzy *c*-means clustering algorithm', *J. Computers & Geosciences* **10**, 191–203.

Birol, G., Doruker, P., Kardar, B., Onsan, Z. dan Ulgen, K. (1998), 'Mathematical description of ethanol fermentation by immobilised *Saccaromyces cerevisiae*', *Process Biochemistry* **7**, 763–771.

Burhenne, S., Jacob, D. dan Henze, G. P. (2011), 'Sampling Based on Sobol Sequences for Monte Carlo Techniques Applied to Building Simulations', *Proceedings of Building Simulation 2011: 12th Conference of International Building Performance Simulation Association, Sydney* .

Cardona, C. A., Quintero, J. A. dan Paz, I. C. (2010), 'Production of bioethanol from sugarcane bagasse: status and perspectives', *Bioresour. Technol.* **101**, 4754–4766.

Cardona, C. A., Sánchez, O. dan Gutiérrez, L. (2009), *Process Synthesis for Fuel Ethanol Production*, Taylor & Francis Inc., United States.

Cazzador, L. (1991), 'Analysis of oscillations in yeast continuous cultures by a new simplified model', *Bull.Math. Biology* **53**, 685–700.

Cazzador, L., Alberghina, L., Martegani, E. dan Mariani, L. (1987), 'Bioreactor control and modeling: A simulation program based on a structured population model of budding yeast', *in: G.W. Moody, P.B. Baker (Eds.), Bioreactors and Biotransformations, Elsevier, London* 64–75.

Christophe, H., Jeremy, S., David, L. dan Bernhard, O. (2001), 'Combining Pathway Analysis with Flux Balance Analysis for the Comprehensive Study of Metabolic Systems', *Biotechnol Bioeng* **71**, 286–306.

Corless, R. M., Gonnet, G. H., Hare, D. E. G., Jeffery, D. J. dan Knuth, D. E. (1996), 'On the Lambert W Function', *Advances in computational mathematics* **5**(4), 329–359.

du Preez, F. B., van Niekerk, D. D., Kooi, B., Rohwer, J. M. dan Snoep, J. L. (2012), 'From steady-state to synchronized yeast glycolytic oscillations I: model construction', *FEBS Journal* **279**(16), 2810–2822.

Duboc, P. dan von Stockar, U. (2000), 'Modeling of oscillating cultivations of *Saccharomyces cerevisiae*: Identification of population structure and expansion kinetics based on on-line measurements', *Chem. Eng. Sci.* **55**, 149–160.

Duda, R. dan Hart, P. (1973), *Pattern classification and scene analysis*, Wiley-Interscience, New York.

Eisenmesser, E., Bosco, D., Akke, M. dan Kern, D. (2002), 'Enzyme dynamics during catalysis', *Science* **295**, 1520–1523.

Gelfand, I. M., Gelfand, I. M., Kapranov, M. dan Zelevinsky, A. (2008), *Discriminants, resultants, and multidimensional determinants*, Springer Science & Business Media.

Goldberg, D. (1989), *Genetic Algorithm in Search, Optimization, and Machine Learning*, Addison-Wesley, New York.

Hale, J. K. (1977), *Theory of functional differential equations*, Springer-Verlag New York.

Heinrich, R. dan Holzh$\ddot{u}$tter, H. (1985), 'Efficiency and design of simple metabolic systems', *Biomed. Biochim. Acta* **44**, 959–969.

Heinrich, R., Holzh$\ddot{u}$tter, H. dan Schuster, S. (1987), 'A theoretical approach to the evolution and structural design of enzymatic networks. Linear enzymatic chains, branched pathways and glycolysis of eryth- rocytes', *Bull. Math. Biol.* **49**, 539–595.

Heinrich, R., Rapoport, S. M. dan Rapoport, T. (1977), 'Metabolic regulation and mathematical models', *Progress in Biophysics & Molecular Biology* **32**, 1–82.

Heinrich, R. dan Schuster, S. (1996), *The Regulation of Cellular Systems*, Chapman & Hall, New York.

Heinrich, R. dan Schuster, S. (1998), 'The modelling of metabolic systems. Structure, control and optimality', *BioSystems* **47**, 61–77.

Heinzle, E., Dunn, I., Furukawa, K. dan Tanner, R. (1982), 'Modelling of sustained oscillations observed in continuous culture of *Saccharomyces cerevisiae*', *in: Proc. IFAC Workshop on Modeling and Control of Biotechnological Processes, Helsinki, Finland* 57–65.

Herschlag, D. (1988), 'The role of induced fit and conformational changes of enzymes in specificity and catalysis', *Biorg. Chem.* **16**, 62–96.

Hinch, R. dan Schnell, S. (2004), 'Mechanism equivalence in enzymesubstrate reactions: Distributed differential delay in enzyme kinetics', *Journal of Mathematical Chemistry* **35**(3), –.

Hjortso, M. dan Bailey, J. (1983), 'Transient responses of budding yeast populations', *Math. Biosci.* **63**, 121–148.

Hoefnagel, M. H. N., Starrenburg, M. J. C., Martens, D. E., Hugenholtz, J., Kleerebezem, M., Swam, I. I. V., Bongers, R., Westerhoff, H. V. dan Snoep, J. L. (2002), 'Metabolic engineering of lactic acid bacteria, the combined approach: kinetic modelling, metabolic control and experimental analysis', *Microbiology* 1003–1013.

Hong, J. (1989), 'Communications to the Editor Yield Coefficients for Cell Mass and Product Formation', *Biotechnology and Bioengineering* **33**, 506–507.

Jones, K. dan Kompala, D. (1999), 'Cybernetic modeling of the growth dynamics of *Saccharomyces cerevisiae* in batch and continuous cultures', *J. Biotechnolgy* **71**, 105–131.

Kargi, F. (2009), 'Re-interpretation of the logistic equation for batch microbial growth in relation to Monod kinetics', *Letters in Applied Microbiology* **48**, 398–401.

Kasbawati, Gunawan, A. Y., Hertadi, R. dan Sidarto, K. A. (2012), 'Aplikasi Metabolic Control Analysis pada percabangan piruvat dalam sistem reaksi fermentasi etanol oleh ragi *Saccharomyces cerevisiae*', *Prosiding Konferensi Nasional Matematika XVI* **-**(-), 1005–1012.

Kasbawati, Gunawan, A. Y., Hertadi, R. dan Sidarto, K. A. (2014a), 'Effects of time delay on the dynamics of a kinetic model of a microbial fermentation process', *the ANZIAM J.* **55**(4), 336–356.

Kasbawati, Gunawan, A. Y., Hertadi, R. dan Sidarto, K. A. (2015a), 'Metabolic Regulation and Maximal Reaction Optimization in the Central Metabolism of A Yeast Cell', *AIP Conference Proceedings* **1651**(-), 75–85.

Kasbawati, Gunawan, A. Y., Sidarto, K. A. dan Hertadi, R. (2015b), 'A New Strategy of Glucose Supply in A Microbial Fermentation Model', *AIP Proceedings (to appear)* **-**(-), –.

Kern, A., Tilley, E., Hunter, I., Legiša, M. dan Glieder, A. (2007), 'Engineering primary metabolic pathways of industrial micro-organisms', *Journal of Biotechnology* **129**, 6–29.

Kirk, D. E. (1998), *Optimal Control Theory: an Introduction*, Dover Publications, Inc., New York.

Klipp, E., Herwig, R., Kowald, A., Wierling, C. dan Lehrach, H. (2005), *Systems Biology in Practice*, Wiley-VCH Verlag, Jerman.

Lei, F., Rotboll, M. dan Jorgensen, S. (2001), 'A biochemically structured model for *Saccaromyces cerevisiae*', *Journal of Biotechnology* **88**, 205–221.

Lewis, F. L. (1986), *Optimal control*, A Wiley-Interscience publication.

Meyer, C. D. (2000), *Matrix analysis and applied linear algebra*, SIAM.

Monod, J. (1942), *Recherches sur la croissance des cultures bacteriennes*, Ed. Hermann and Cie.

Murray, J. (1990), *Mathematical biology, biomathematics texts*, 2 edn, Springer-Verlag, New York.

Mussato, S., Dragone, G., Guimaraes, P., Silva, J., Carneiro, L., Roberto, I., Vicente, A., Domingues, L. dan Teixeira, J. (2010), 'Technological trends, global market, and challenges of bio-ethanol production', *Biotechnol. Adv.* –.

Nelson, D. L. dan Cox, M. M. (2005), *Lehninger: Principles of biochemistry*, fourth edition edn, Whfreeman, Madison.

Nielsen, J. (1998), 'Cellular and metabolic engineering', *Biotechnol. Bioeng.* **58**, 125–132.

Nielsen, J. dan Olsson, L. (2002), 'An expanded role for microbial physiology in metabolic engineering and functional genomics:moving towards systems biology', *FEMS Yeast Res.* **2**, 175–181.

O'Brien, D. J. dan Craig, J. C. J. (1996), 'Ethanol production in a continuous fermentation/membrane pervaporation system', *Applied Microbiology and Biotechnology* **44**(6), 699–704.

Ojeda, K., Ávila, O., Suárez, J. dan Kafarov, V. (2010), 'Evaluation of technological alternatives for process integration of sugarcan bagasse for sustainable biofuels production part 1', *Chem. Eng. Res. Des.* doi:10.1016/j.cherd.2010.07.007.

Palmer, T. (1995), *Understanding Enzymes*, 4 edn, Prentice Hall-Ellis Horwood, London.

Parwata, I. P., Asyari, M. dan Hertadi, R. (2014), 'Organic Solvent-Stable Lipase from Moderate Halophilic Bacteria Pseudomonas stutzeri Isolated from the Mud Crater of Bleduk Kuwu, Central Java, Indonesia', *J. of Pure and Applied Microbiology* **8**, 31–40.

Pham, H. T. B., Larsson, G. dan Enfors, S. (1998), 'Growth and energy metabolism in aerobic fed-batch cultures of *Saccharomyces cerevisiae*: Simulation and model verification', *Biotechnology and Bioengineering* **60**, 1097–0290.

Postma, E., Verduyn, C., Scheffers, W. A. dan van Dijken, J. P. (1989), 'Enzymic Analysis of the Crabtree Effect in Glucose-Limited Chemostat Cultures of *Saccharomyces cerevisiae*', *Applied and environmental microbiology* **55**(2), 468–477.

Pronk, J., Steensma, H. Y. dan Dijken, J. V. (1996), 'Pyruvat Metabolism in *Saccharomyces cerevisiae*', *Yeast* **12**, 1607–1633.

Reder, C. (1998), 'Metabolic control theory: a structural approach', *J. Theor. Biol.*

135, 175–201.

Rizzi, M., Baltes, M., Theobald, U. dan Reuss, M. (1997), ‘In Vivo Analysis of Metabolic Dynamics in *Saccharomyces cerevisiae*: II Mathematical Model’, *Biotechnology and Bioengineering* **55**(4), 592–608.

Rizzi, M., Theobald, U., Querfurth, E., Rohrhirsch, T., Bakes, M. dan Reuss, M. (1996), ‘In Vivo Investigations of Glucose Transport in *Saccharomyces cerevisiae*’, *Biotechnology and Bioengineering* **49**(3), 316–327.

Roussel, M. R. (1996), ‘The Use of Delay Differential Equations in Chemical Kinetics’, *J. Phys. Chem.* **100**, 8323–8330.

Schomburg, I., Chang, A., Placzek, S., Söhngen, C., Rother, M., Lang, M., Munaretto, C., Ulas, S., Stelzer, M., Grote, A., Scheer, M. dan Schomburg, D. (2013), ‘BRENDA in 2013: integrated reactions, kinetic data, enzyme function data, improved disease classification: new options and contents in BRENDA’, *Nucleic Acids Res.* **41**, D764–772.

Shampine, L. F. dan Thompson, S. (2001), ‘Solving DDEs in M ATLAB’, *Applied Numerical Mathematics* **37**, 441–458.

Shuler, M. L. dan Kargi, F. (2002), *Bioprocess Engineering*, - edn, Prentice Hall PTR.

Sánchez, O. dan Cardona, C. (2008), ‘Trends in biotechnological production of fuel ethanol from different feedstocks’, *Bioresour. Technol.* **99**, 5270–5295.

Sonnleitner, B. dan Kappeli, O. (1986), ‘Growth of *Saccaromyces cerevisiae* Is Controlled by Its Limited Respiratory Capacity: Formulation and Verification of a Hypothesis’, *Bio. & Bioeng.* **28**, 927–937.

Storn, R. dan Price, K. (1997), ‘Differential Evolution - A Simple and Efficient Heuristic for Global Optimization over Continuous Spaces’, *Journal of Global Optimization* **11**, 341359.

Strassle, C., Sonnleitner, B. dan Fiechter, A. (1988), ‘A predictive model for the spontaneous synchronization of *Saccharomyces cerevisiae* grown in continuous culture’, *I. Concept, J. Biotechnol.* **7**, 299–318.

Taber, R. L., Campbell, A. dan Spencer, S. (1998), ‘A simple experiment demonstrating the allosteric regulation of yeast pyruvate kinase’, **26**, 73–76.

Theobald, U., Mailinger, W., Baltes, M., Rizzi, M. dan Reuss, M. (1997), ‘In Vivo Analysis of Metabolic Dynamics in *Saccharomyces cerevisiae*: I. Experimental Observations’, *Biotechnology and Bioengineering* **55**(2), 305–316.

Vásquez-Bahena, J., Montes-Horcasitas, M. C., Ortega-López, J., Magaña-Plaza, I. dan Flores-Cotera, L. B. (2004), ‘Multiple steady states in a continuous stirred tank reactor: An experimental case study for hydrolysis of sucrose by invertase’, *Process Biochemistry* **39**, 2179–2182.

Valentini, G., Chiarelli, L., Fortin, R., Speranza, M. L., Galizzi, A. dan Mattevi, A. (2000), ‘The Allosteric Regulation of Pyruvate Kinase’, **275**(24), 18145–18152.

van Heerden, J. H., Wortel, M. T., Bruggeman, F. J., Heijnen, J. J., Bollen, Y. J. M., Planque, R., Hulshof, J., O'Toole, T. G., a. Wahl, S. dan Teusink, B. (2014), 'Lost in Transition: Start-Up of Glycolysis Yields Subpopulations of Nongrowing Cells', *Science* **343**, 1245114–1245114.

Xiu, Z. L., Song, B. H., Sun, L. H. dan Zeng, A. P. (2002), 'Theoretical analysis of effects of metabolic overflow and time delay on the performance and dynamic behavior of a two-stage fermentation process', *Biochemical Engineering Journal* **11**, 101–109.

Yang, X. dan Deb, S. (2009), 'Cuckoo search via Lévy flights', *World Congress on Nature & Biologically Inspired Computing (NaBIC 2009), IEEE Publications* 210–214.

Yang, X. dan Deb, S. (2010), 'Engineering optimisation by cuckoo search', *International Journal of Mathematical Modelling and Numerical Optimisation* **1**(4), 330–343.

Yang, X. dan Deb, S. (2013), 'Multiobjective cuckoo search for design optimization', *Computers & Operations Research* **40**(6), 1616–1624.

Yi, S., Nelson, P. W. dan Ulsoy, A. G. (2010), *Analysis and control using the Lambert W function, Time-delay sistems*, World Scientific.

INDEKS

RIWAYAT HIDUP

Penulis dilahirkan di Watampone Kabupaten Bone Sulawesi Selatan pada tanggal 4 September 1980 dari orang tua Alm. Muh. Tahir S. dan Hj. Wahida. Penulis merupakan anak terakhir dari sembilan bersaudara. Penulis menempuh pendidikan dasar hingga menengah di Watampone, yaitu MI Saliweng Benteng (1986-1992), SMPN I Watampone (1992-1995), dan SMUN I Watampone (1995-1998). Pada tahun 1998, Penulis diterima sebagai mahasiswa Program Sarjana di Jurusan Matematika FMIPA Universitas Hasanuddin dan memperoleh gelar Sarjana pada tahun 2002. Setelah menyelesaikan pendidikan Program Sarjana, pada tahun 2003 Penulis diterima menjadi anggota staf pengajar di Jurusan Matematika FMIPA Universitas Hasanuddin.

Pada tahun 2005 Penulis mendapatkan kesempatan untuk melanjutkan pendidikan Magister di Program Studi Magister Matematika Institut Teknologi Bandung melalui pendanaan Beasiswa Program Pasca Sarjana (BPPS) DIKTI. Penulis memperoleh gelar Master Sains pada tahun 2007. Pada tahun 2011, Penulis kemudian melanjutkan pendidikan Doktor di Program Doktor Matematika, Institut Teknologi Bandung, melalui pendanaan beasiswa yang sama yaitu BPPS yang sekarang berganti nama menjadi BPPDN. Selama masa Program Doktor, Penulis mendapatkan kesempatan untuk mengikuti Program *Sandwich* (PKPI) yang didanai oleh DIKTI pada bulan Agustus sampai November tahun 2013 di grup Biometris, Plant Sciences, Wageningen University and Research Center (WUR), Belanda, dibawah bimbingan Prof. Dr. Jaap Molenaar dan Dr. Maarten de Gee. Selama Program *Sandwich*, Penulis juga mendapatkan kesempatan untuk mengikuti *Workshop Interdisciplinary Life Sciences* di Lorentz Center, Leiden University, Belanda.

Selama mengikuti Program Doktor, Penulis telah menghasilkan beberapa artikel ilmiah yang sebagian telah diterbitkan. Penulis juga aktif mengikuti beberapa pertemuan dan kegiatan ilmiah.

Daftar artikel yang telah dipublikasikan:

1. **Kasbawati**, A. Y. Gunawan, R. Hertadi, K. A. Sidarto (2012): Aplikasi Metabolic Control Analysis pada Percabangan Piruvat dalam Sistem Reaksi Fermentasi Etanol oleh Sel Ragi *S. cerevisiae*, *Prosiding Konferensi Nasional Matematika XVI*, Hal. 1005-1012, ISBN No. 978-602-19590-2-2.

2. **Kasbawati**, A. Y. Gunawan, R. Hertadi, K. A. Sidarto (2014): Effects of Time Delay on the Dynamics of a Kinetic Model of Microbial Fermentation Process, *the ANZIAM Journal*, Cambridge, Vol. 55, No. 4, Hal. 336-356, doi:10.1017/S1446181114000194.
3. **Kasbawati**, A. Y. Gunawan, R. Hertadi, K. A. Sidarto (2015): Metabolic Regulation and Maximal Reaction Optimization in the Central Metabolism of a Yeast Cell, *AIP Conference Proceedings*, Vol. 1651, Hal. 75-85, doi: 10.1063/1.4914436.
4. **Kasbawati**, A. Y. Gunawan, K. A. Sidarto, R. Hertadi (2015): A New Strategy of Glucose Supply in a Microbial Fermentation Model, *AIP Conference Proceedings* (*to appear*).

Daftar artikel lainnya:

1. A.Y. Gunawan, **Kasbawati**, K.A. Sidarto: Approximate Solutions of Linearized Delay Differential Equations Arising from a Microbial Fermentation Process Using the Matrix Lambert Function (telah dikirim ke *J. of Math. & Fund. Sciences*).
2. **Kasbawati**, A. Y. Gunawan, K. A. Sidarto, R. Hertadi: Optimizing Ethanol Production in a Microbial Fermentation Model Using an On-Off Feeding Strategy (telah dikirim ke *International Journal of Biomathematics*, World Scientific).

Publikasi lainnya:

Akudibillah G, Boas SEM, Carreres BM, Dallinga M, van Dijk A, Gupta SK, Hunt A, Jacobsen A, **Kasbawati**, Merks RRMH, Molenaar J, Overal GG, Palm M, Perenboom MJ, Prasad M, Reijnders M, Rens EG, Ryback BM, Scheider L, Srivastava M, Willemsen MAM, Wu X, Zagaris A. (2014) Scientific report: Training workshop interdisciplinary life sciences. *PeerJ PrePrints* 2:e654v1, http://dx.doi.org/10.7287/peerj.preprints.654v1.

Kunjungan penelitian:

Visiting Academic, *Biometris Group, Plant Sciences, Wageningen University and Research Center, Wageningen, Belanda*, 28 Agustus - 27 November 2013.

Daftar seminar dan konferensi yang pernah diikuti:

1. Kasbawati, Aplikasi Metabolic Control Analysis pada Percabangan Piruvat

dalam Sistem Reaksi Fermentasi Etanol oleh Sel Ragi *Saccharomyces Cerevisiae*, *Konferensi Nasional Matematika (KNM) XVI*, Universitas Padjadjaran, Jatinangor, Bandung, 6 Juli 2012.

2. Kasbawati, Effect of Time Delay on the Dynamic Behavior of a Kinetic Model of a Branched Metabolic Pathway, *The* 4^{th} *International Conference on Mathematics and Natural Sciences (ICMNS)*, ITB, Bandung, 8-9 November 2012.
3. Kasbawati, Regulation Analysis of Enzyme Activity Inhibition in a Microbial Fermentation Process, *The* 9^{th} *East Asia SIAM Conference and The* $2^{n}d$ *Conference on Industrial and Applied Mathematics (EASIAM-CIAM)*, The Newton Hotel, Bandung, 18-20 Juni 2013.
4. Kasbawati, Optimization of Ethanol Production in a Yeast Continuous Fermentation Process with Reducing the Flux of an Alternative Pathway, *International Conference on Computer Engineering and Mathematical Sciences (ICCEMS)*, Kuala Lumpur, Malaysia, 5-6 Desember 2013.
5. Kasbawati, Optimizing the Maximal Activity of Enzymes in a Microbial Fermentation Model, *East Asia SIAM Conference (EASIAM)*, Ambassador City Jomtien, Pattaya, Thailand, 23-25 Juni, 2014.
6. Kasbawati, Metabolic Regulation and Maximal Reaction Optimization in the Central Metabolism of a Yeast Cell, *International Symposium on Biomathematics (SYMOMATH)*, Malang, 31 Agustus-2 September, 2014.
7. Kasbawati, A New Strategy of Glucose Supply in a Microbial Fermentation Model, *The* 5^{th} *International Conference on Mathematics & Natural Sciences (ICMNS)*, ITB, Bandung, 2-3 November 2014.
8. Kasbawati, Approximate Solutions of Linearized Delay Differential Equations Arising from a Microbial Fermentation Process Using the Matrix Lambert Function, *The* 2^{nd} *International Conference on Mathematics and Statistics (ICMSC)*, Ho Chi Minh, Vietnam, 28-29 Agustus 2015.

Daftar kegiatan ilmiah lainnya yang pernah diikuti:

1. Peserta pada *Pelatihan Penulisan Artikel Ilmiah untuk Publikasi di Jurnal Internasional*, ITB, 11 November 2011.
2. Peserta pada *Seminar Kaitan antara Dinamika Iklim dalam Pemodelan Matematika*, ITB, 10 Desember 2011.
3. Peserta pada *Workshop on Numerical Methods for Differential Equations*, ITB, 14-20 Maret 2012.
4. Peserta pada *Compact Course on Mathematical Modelling*, ITB, 3-7 September 2012.
5. Peserta pada *Workshop on Mathematical Modelling 2012: Corrosion Inhibition in Steel Pipes Used in the Oil Industry*, ITB, 17-20 September 2012.

6. Peserta pada *APEC Workshop on Promoting Best Practices on Mathematical Modelling Course*, ITB, 22-23 Oktober 2012.
7. Peserta pada *Workshop Biomathematic 2012*, Wisma UNPAD, 1 Desember 2012.
8. Peserta pada *Compact Course on Numerical Methods for Partial Differential Equations*, ITB, 8-11 April 2013.
9. Peserta pada *Compact Course on Stochastic Analysis*, ITB, 15-18 April 2013.
10. Peserta pada *Training Workshop Interdisciplinary Life Sciences*, Lorentz Center, Leiden University, Leiden, Belanda, 21 - 25 Oktober 2013.
11. Peserta pada *Compact Course: Some Aspects of Interacting Particle Systems*, ITB, 17-19 November 2014.
12. Peserta pada *Workshop on Biomathematics and Math. Finance*, ITB, 25-29 Mei 2015.

Lampiran A Persamaan Kinetika Michaelis-Menten untuk Reaksi *Reversible*

Tinjau reaksi kelima dalam Gambar I.2 dengan mekanisme *reversible*, yaitu

$$s_5 + e_5 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} e_5 s_5 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} e_5 + s_7.$$

Pada reaksi ke kanan (*forward reaction*), enzim e_5 mengkatalis konversi substrat s_5 menjadi s_7. Begitupula pada reaksi sebaliknya (*backward reaction*). Dinamika dari reaksi tersebut dimodelkan sebagai berikut:

$$\frac{ds_5}{dt} = k_{-1}e_5s_5 - k_1e_5 \cdot s_5, \tag{A.1a}$$

$$\frac{de_5s_5}{dt} = -(k_{-1} + k_2)e_5s_5 + (k_1s_5 + k_{-2}s_7)e_5, \tag{A.1b}$$

$$\frac{de_5}{dt} = (k_{-1} + k_2)e_5s_5 - (k_1s_5 + k_{-2}s_7)e_5, \tag{A.1c}$$

$$\frac{ds_7}{dt} = k_2e_5s_5 - k_{-2}e_5 \cdot s_7, \tag{A.1d}$$

dengan konstanta laju reaksi k_i. Laju reaksi r_6 adalah

$$r_6 = -\frac{ds_5}{dt} = \frac{ds_7}{dt}. \tag{A.2}$$

Untuk menyelesaikan Persamaan (A.2), beberapa asumsi digunakan untuk menyederhanakan sistem reaksi tersebut. Briggs dan Haldane (1925) mengasumsikan bahwa selama reaksi berlangsung terdapat waktu tertentu yang membuat kondisi setimbang dicapai pada tahap transisi (tahap pembentukan enzim kompleks e_5s_5). Kondisi tersebut dinamakan kondisi *quasi-steady state* (lihat Klipp dkk. (2005)), yang secara matematika dituliskan sebagai berikut:

$$\frac{de_5s_5}{dt} = 0. \tag{A.3}$$

Karena pada reaksi tersebut enzim tidak diproduksi ataupun dikonsumsi maka total konsentrasinya selalu konstan, yaitu $e_5^t = e_5 + e_5s_5$. Akibatnya diperoleh

$$\frac{de_5}{dt} = 0. \tag{A.4}$$

Dari Persamaan (A.1b) dan (A.1c), dengan menggunakan (A.3) dan (A.4), diperoleh

$$e_5 = \frac{(k_{-1} + k_2)e_5^t}{k_1s_5 + k_{-2}s_7 + (k_{-1} + k_2)}, \tag{A.5}$$

dan

$$e_5 s_5 = \frac{(k_1 s_5 + k_{-2} s_7) e_5^t}{k_1 s_5 + k_{-2} s_7 + (k_{-1} + k_2)}. \tag{A.6}$$

Substitusi Persamaan (A.5) dan (A.6) ke (A.2) menghasilkan

$$\begin{aligned} r_6 &= k_2(e_5 s_5) - k_{-2} \cdot e_5 \cdot s_7 \\ &= \frac{k_2(k_1 s_5 + k_{-2} s_7) e_5^t}{k_1 s_5 + k_{-2} s_7 + (k_{-1} + k_2)} - \frac{k_{-2}(k_{-1} + k_2) e_5^t s_7}{k_1 s_5 + k_{-2} s_7 + (k_{-1} + k_2)}. \end{aligned} \tag{A.7}$$

Jika Persamaan (A.7) dituliskan kembali dalam v_{5f}, v_{5b}, k_{5f}, dan k_{5b}, dengan $v_{5f} = k_2 e_5^t$, $v_{5b} = k_{-1} e_5^t$, $k_{5f} = \frac{k_{-1}+k_2}{k_1}$, dan $k_{5b} = \frac{k_{-1}+k_2}{k_{-2}}$, maka diperoleh laju reaksi untuk reaksi *reversible*, yaitu

$$\begin{aligned} r_6 &= \frac{v_{5f} k_{5b} s_5(t) - v_{5b} k_{5f} s_7(t)}{k_{5f} k_{5b} + k_{5b} s_5(t) + k_{5f} s_7(t)} \\ &= \frac{v_{5f} s_5}{k_{5f} + s_5 + (k_{5f}/k_{5b})\, s_7} - \frac{v_{5b} s_7}{k_{5b} + s_7 + (k_{5b}/k_{5f})\, s_5} \\ &= r_6^f - r_6^b. \end{aligned} \tag{A.8}$$

Konstanta v_{5f} dan v_{5b}, secara berturut-turut, menyatakan laju reaksi maksimum untuk reaksi ke kanan (*forward reaction*) dan sebaliknya (*backward reaction*). Sedangkan konstanta k_{5f} dan k_{5b}, secara berturut-turut, menyatakan konstanta Michaelis untuk masing-masing reaksi. Dalam kedua kasus reaksi tersebut, keterlibatan s_5 dan s_7 pada suku penyebutnya menunjukkan bahwa s_5 dan s_7 saling berkompetisi untuk enzim yang sama. Jadi setiap 'substrat' menunjukkan efek saling inhibisi secara kompetitif. Jika $s_5 = 0$ atau $s_7 = 0$ maka persamaan untuk r_6^f atau r_6^b menghasilkan persamaan kinetika Michaelis-Menten untuk reaksi yang *irreversible*.

Lampiran B Syarat Perlu Keoptimalan dari Fungsi Lagrange L

Tinjau fungsi Lagrange dalam Persamaan (3.38). Persamaan tersebut dapat dituliskan kembali menjadi

$$L(\boldsymbol{y},\boldsymbol{p},\boldsymbol{q}) = \int_0^1 \{y_7(\tilde{t},\boldsymbol{q}) + \sum_{i=1}^{7}[p_i(\tilde{t})f_i(\boldsymbol{y},\tilde{u}) - p_i(\tilde{t})\dot{y}_i(\tilde{t},\boldsymbol{q})] + p_8(\tilde{t})\Theta(\tilde{u})\}\, d\tilde{t}. \tag{B.1}$$

Diketahui

$$\frac{d}{d\tilde{t}}\left[p(\tilde{t})y(\tilde{t},\boldsymbol{q})\right] = \dot{p}(\tilde{t})y(\tilde{t},\boldsymbol{q}) + p(\tilde{t})\dot{y}(\tilde{t},\boldsymbol{q}),$$

sehingga diperoleh

$$p(\tilde{t})\dot{y}(\tilde{t},\boldsymbol{q}) = -\dot{p}(\tilde{t})y(\tilde{t},\boldsymbol{q}) + \frac{d}{d\tilde{t}}\left[p(\tilde{t})y(\tilde{t},\boldsymbol{q})\right]. \tag{B.2}$$

Jika Persamaan (B.2) digunakan pada Persamaan (B.1) maka diperoleh

$$\begin{aligned}
&L(\boldsymbol{y},\boldsymbol{p},\boldsymbol{q})\\
&= \int_0^1 \{y_7(\tilde{t},\boldsymbol{q}) + \sum_{i=1}^{7}[p_i(\tilde{t})f_i(\boldsymbol{y},\tilde{u}) + \dot{p}_i(\tilde{t})y_i(\tilde{t},\boldsymbol{q}) - \frac{d}{d\tilde{t}}(p_i(\tilde{t})y_i(\tilde{t},\boldsymbol{q}))] + p_8(\tilde{t})\Theta(\tilde{u})\}\, d\tilde{t}\\
&= \int_0^1 \{y_7(\tilde{t},\boldsymbol{q}) + \sum_{i=1}^{7}[p_i(\tilde{t})f_i(\boldsymbol{y},\tilde{u}) + \dot{p}_i(\tilde{t})y_i(\tilde{t},\boldsymbol{q})] + p_8(\tilde{t})\Theta(\tilde{u})\}\, d\tilde{t}\\
&\quad - \sum_{i=1}^{7}\{p_i(1)y_i(1,\boldsymbol{q}) - p_i(0)y_i(0,\boldsymbol{q})\}.
\end{aligned} \tag{B.3}$$

Syarat perlu keoptimalan fungsi objektif (3.36) menyatakan bahwa solusi optimalnya merupakan titik stasioner dari fungsional L, $\nabla L(\boldsymbol{y},\boldsymbol{p},\boldsymbol{q}) = \mathbf{0}$, dengan ∇ adalah sebuah operator gradien (Lewis, 1986; Kirk, 1998). Dari persamaan $\partial L/\partial \boldsymbol{p} = \mathbf{0}$ diperoleh sistem metabolisme,

$$\dot{\boldsymbol{y}} = \boldsymbol{f}(\boldsymbol{y},\tilde{u}),\;\; \boldsymbol{y}(0) = \boldsymbol{y}_0,$$

dan konstrain $\Theta(\tilde{u}) = 0$. Selanjutnya, jika Persamaan (B.3) diturunkan secara parsial terhadap $y_j,\; j = 1\cdots,7$, diperoleh

$$\begin{aligned}
&\frac{\partial}{\partial y_j}L(\boldsymbol{y},\boldsymbol{p},\boldsymbol{q})\\
&= \int_0^1 \frac{\partial}{\partial y_j}\{y_7(\tilde{t},\boldsymbol{q}) + \sum_{i=1}^{7}[p_i(\tilde{t})f_i(\boldsymbol{y},\tilde{u}) + \dot{p}_i(\tilde{t})y_i(\tilde{t},\boldsymbol{q})] + p_8(\tilde{t})\Theta(\tilde{u})\}\, d\tilde{t}\\
&\quad - \frac{\partial}{\partial y_j}\sum_{i=1}^{7}\{p_i(1)y_i(1,\boldsymbol{q}) - p_i(0)y_i(0,\boldsymbol{q})\}
\end{aligned}$$

$$= \int_0^1 \{\frac{\partial}{\partial y_j}[y_7(\tilde{t},\boldsymbol{q}) + \sum_{i=1}^{7} p_i(\tilde{t}) f_i(\boldsymbol{y},\tilde{u})] + \sum_{i=1}^{7} \dot{p}_i(\tilde{t}) \frac{\partial}{\partial y_j} y_i(\tilde{t},\boldsymbol{q})\}\, d\tilde{t}$$
$$- \sum_{i=1}^{7} \{p_i(1)\frac{\partial}{\partial y_j} y_i(1,\boldsymbol{q}) - p_i(0)\frac{\partial}{\partial y_j} y_i(0,\boldsymbol{q})\}.$$

Diketahui
$$\frac{\partial}{\partial y_j} y_i(\tilde{t},\boldsymbol{q}) = \begin{cases} 0, & \text{jika } i \neq j, \\ 1, & \text{jika } i = j, \end{cases}$$

sehingga diperoleh

$$\begin{aligned} \frac{\partial}{\partial y_j} L(\boldsymbol{y},\boldsymbol{p},\boldsymbol{q}) = & \int_0^1 \{\frac{\partial}{\partial y_j}[y_7(\tilde{t},\boldsymbol{q}) + \sum_{i=1}^{7} p_i(\tilde{t}) f_i(\boldsymbol{y},\tilde{u})] + \dot{p}_j(\tilde{t})\}\, d\tilde{t} \\ & - \sum_{i=1}^{7} \{p_i(1)\frac{\partial}{\partial y_j} y_i(1,\boldsymbol{q}) - p_i(0)\frac{\partial}{\partial y_j} y_i(0,\boldsymbol{q})\}, \end{aligned}$$

untuk setiap $j = 1, \cdots, 7$. Persamaan $\partial L/\partial y_j = 0$ dipenuhi jika

$$\dot{p}_j = g_j(\boldsymbol{y},\boldsymbol{p}), \tag{B.4}$$

dengan $g_j = -\frac{\partial}{\partial y_j}(y_7 + \sum_{i=1}^{7} p_i f_i)$, yaitu

$$\begin{aligned} g_1 &= \frac{\omega_1\theta_1(p_1 - p_2)}{(\theta_1 + y_1)^2}, \\ g_2 &= p_2 \sum_{i=2}^{4} \frac{\omega_i\theta_i}{(\theta_i + y_2)^2} - \sum_{i=2}^{4} p_{i+1} \frac{\omega_i\theta_i}{(\theta_i + y_2)^2}, \\ g_3 &= p_3\sigma_1, \\ g_4 &= p_4\sigma_2, \\ g_5 &= (p_5 - p_7)\left(\frac{\theta_{5b}\theta_{5f}(\omega_{5f}\theta_{5b} + \omega_{5f}y_7 + \omega_{5b}y_7)}{(\theta_{5f}\theta_{5b} + \theta_{5b}y_5 + \theta_{5f}y_7)^2}\right) + (p_5 - p_6)\frac{\omega_6\theta_6}{(\theta_6 + y_5)^2}, \\ g_6 &= (p_6 - p_4)\frac{\omega_7\theta_7}{(\theta_7 + y_6)^2} + p_6\sigma_3, \\ g_7 &= -1 - (p_5 - p_7)\left(\frac{\theta_{5f}\theta_{5b}(\omega_{5b}\theta_{5f} + \omega_{5b}y_5 + \omega_{5f}y_5)}{(\theta_{5f}\theta_{5b} + \theta_{5b}y_5 + \theta_{5f}y_7)^2}\right) + p_7\sigma_4, \end{aligned}$$

dan
$$p_i(1)\frac{\partial}{\partial y_j} y_i(1,\boldsymbol{q}) - p_i(0)\frac{\partial}{\partial y_j} y_i(0,\boldsymbol{q}) = 0. \tag{B.5}$$

Karena sistem metabolisme yang dimodelkan memiliki nilai awal yang tetap dan nilai akhir yang bebas, maka diperoleh $\partial y_i(0,\boldsymbol{q})/\partial y_j = 0$ dan $\partial y_i(1,\boldsymbol{q})/\partial y_j \neq 0$ untuk $i = j$. Jadi Persamaan (B.5) dipenuhi jika $p_i(1) = 0$ untuk setiap $i = j$. Selanjutnya, jika Persamaan (B.3) diturunkan secara parsial terhadap q_k, $k = 1, 2$, diperoleh

$$\frac{\partial}{\partial q_k} L(\boldsymbol{y}, \boldsymbol{p}, \boldsymbol{q})$$

$$= \int_0^1 \{ \frac{\partial}{\partial q_k} y_7(\tilde{t}, \boldsymbol{q}) + \overbrace{\frac{\partial}{\partial q_k} \sum_{i=1}^{7} [p_i(\tilde{t}) f_i(\boldsymbol{y}, \tilde{u}) + \dot{p}_i(\tilde{t}) y_i(\tilde{t}, \boldsymbol{q})]}^{(*)} + p_8(\tilde{t}) \frac{\partial}{\partial q_k} \Theta(\tilde{u}) \} \, d\tilde{t}$$
$$- \sum_{i=1}^{7} \{ p_i(1) \frac{\partial}{\partial q_k} y_i(1, \boldsymbol{q}) - p_i(0) \frac{\partial}{\partial q_k} y_i(0, \boldsymbol{q}) \}. \tag{B.6}$$

Tinjau bagian $(*)$ dari Persamaan (B.6), yaitu

$$\frac{\partial}{\partial q_k} \sum_{i=1}^{7} [p_i(\tilde{t}) f_i(\boldsymbol{y}, \tilde{u}) + \dot{p}_i(\tilde{t}) y_i(\tilde{t}, \boldsymbol{q})].$$

Jika bentuk tersebut diuraikan diperoleh

$$\frac{\partial}{\partial q_k} [p_1(\tilde{t}) f_1(\boldsymbol{y}, \tilde{u}) + \cdots + p_7(\tilde{t}) f_7(\boldsymbol{y}, \tilde{u}) + \dot{p}_1(\tilde{t}) y_1(\tilde{t}, \boldsymbol{q}) + \cdots + \dot{p}_7(\tilde{t}) y_7(\tilde{t}, \boldsymbol{q})]$$
$$= p_1(\tilde{t}) \sum_{i=1}^{7} \frac{\partial}{\partial y_i} f_1(\boldsymbol{y}, \tilde{u}) \frac{\partial}{\partial q_k} y_i(\tilde{t}, \boldsymbol{q}) + \cdots + p_7(\tilde{t}) \sum_{i=1}^{7} \frac{\partial}{\partial y_i} f_7(\boldsymbol{y}, \tilde{u}) \frac{\partial}{\partial q_k} y_i(\tilde{t}, \boldsymbol{q}) +$$
$$p_1(\tilde{t}) \frac{\partial}{\partial \tilde{u}} f_1(\boldsymbol{y}, \tilde{u}) \frac{\partial \tilde{u}}{\partial q_k} + \cdots + p_7(\tilde{t}) \frac{\partial}{\partial \tilde{u}} f_7(\boldsymbol{y}, \tilde{u}) \frac{\partial \tilde{u}}{\partial q_k} +$$
$$\dot{p}_1(\tilde{t}) \frac{\partial}{\partial q_k} y_1(\tilde{t}, \boldsymbol{q}) + \cdots + \dot{p}_7(\tilde{t}) \frac{\partial}{\partial q_k} y_7(\tilde{t}, \boldsymbol{q})$$
$$= \frac{\partial}{\partial q_k} y_1(\tilde{t}, \boldsymbol{q}) \left[\dot{p}_1(\tilde{t}) + \sum_{i=1}^{7} p_i(\tilde{t}) \frac{\partial}{\partial y_1} f_i(\boldsymbol{y}, \tilde{u}) \right] + \cdots +$$
$$\frac{\partial}{\partial q_k} y_7(\tilde{t}, \boldsymbol{q}) \left[\dot{p}_7(\tilde{t}) + \sum_{i=1}^{7} p_i(\tilde{t}) \frac{\partial}{\partial y_7} f_i(\boldsymbol{y}, \tilde{u}) \right] +$$
$$\frac{\partial \tilde{u}}{\partial q_k} \left[p_1(\tilde{t}) \frac{\partial}{\partial \tilde{u}} f_1(\boldsymbol{y}, \tilde{u}) + \cdots + p_7(\tilde{t}) \frac{\partial}{\partial \tilde{u}} f_7(\boldsymbol{y}, \tilde{u}) \right]$$
$$= \sum_{j=1}^{7} \frac{\partial}{\partial q_k} y_j(\tilde{t}, \boldsymbol{q}) \left[\dot{p}_j(\tilde{t}) + \frac{\partial}{\partial y_j} \sum_{i=1}^{7} p_i(\tilde{t}) f_i(\boldsymbol{y}, \tilde{u}) \right] + \frac{\partial \tilde{u}}{\partial q_k} \frac{\partial}{\partial \tilde{u}} \sum_{i=1}^{7} p_i(\tilde{t}) f_i(\boldsymbol{y}, \tilde{u}). \tag{B.7}$$

Jika bentuk terakhir dari (B.7) disubstitusi ke (B.6) maka, melalui beberapa penyederhanaan, diperoleh

$$\frac{\partial}{\partial q_k} L(\boldsymbol{y}, \boldsymbol{p}, \boldsymbol{q})$$
$$= \int_0^1 \left\{ \sum_{j=1}^{7} \frac{\partial y_j(\tilde{t}, \boldsymbol{q})}{\partial q_k} \left[\dot{p}_j(\tilde{t}) + \frac{\partial}{\partial y_j} \left(y_7(\tilde{t}, \boldsymbol{q}) + \sum_{i=1}^{7} p_i(\tilde{t}) f_i(\boldsymbol{y}, \tilde{u}) \right) \right] + \right.$$

$$\frac{\partial \tilde{u}}{\partial q_k}\left[\frac{\partial}{\partial \tilde{u}}\left(\sum_{i=1}^{7} p_i(\tilde{t}) f_i(\boldsymbol{y}, \tilde{u})\right) + p_8(\tilde{t})\frac{\partial \Theta(\tilde{u})}{\partial \tilde{u}}\right]\Bigg\}\, d\tilde{t} -$$

$$\sum_{i=1}^{7}\{p_i(1)\frac{\partial}{\partial q_k} y_i(1, \boldsymbol{q}) - p_i(0)\frac{\partial}{\partial q_k} y_i(0, \boldsymbol{q})\}.$$

Karena $\frac{\partial y_j}{\partial q_k} \neq 0$ dan $\frac{\partial \tilde{u}}{\partial q_k} \neq 0$ maka diperoleh syarat agar $\partial L/\partial q_k = 0$ dipenuhi, yaitu jika sistem dalam Persamaan (B.4) beserta syarat batasnya $p_j(1) = 0$ dipenuhi dan $\frac{\partial}{\partial \tilde{u}}\left(p_8\Theta(\tilde{u}) + \sum_{i=1}^{7} p_i f_i\right) = 0$ dipenuhi. Jadi diperoleh,

$$\frac{\partial L}{\partial \boldsymbol{q}} = \begin{pmatrix} \dfrac{\partial L}{\partial q_1} \\ \dfrac{\partial L}{\partial q_2} \end{pmatrix} = \begin{pmatrix} p_1 + p_8 \\ p_8 \end{pmatrix} = \mathbf{0},$$

dengan $q_1 = \tilde{S}_g$ dan $q_2 = \phi$.

Info cetak .....

Revisi/cetak terakhir: 4 September 2015, pukul 22:12

Nomor halaman: i–xix,   1–96   Total: 115 halaman